The following compounds are prepared from starting materials obtained as described in Examples 69-71 using the methods described above.

Example	Name	m/z [M+H]
746	4-(6-Chloro-1H-benzoimidazol-2-ylmethyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	395, 397
747	4-(5'-Chloro-[2,2']bithiophenyl-5-ylmethyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	443, 445
748	4-[3-(5-Chloro-thiophen-2-yl)-allyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	386, 388
749	4-(5-Chloro-1H-indol-2-ylmethyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	394, 396
750	4-(6-Chloro-naphthalen-2-ylmethyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	405, 407
751	4-(7-Chloro-isoquinolin-3-ylmethyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	406, 408
752	4-(5'-Chloro-[2,2']bithiophenyl-5-ylmethyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(±)-carboxylic acid methyl ester	501, 503
753	1-(5-Chloro-1H-indol-2-ylmethyl)-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(±)-carboxylic acid methyl ester	452, 454
754	1-[(5-Chloro-thiophen-2-yloxy)-acetyl]-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester	463, 465
755	1-(6-Chloro-benzo[b]thiophene-2-carbonyl)-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester	483, 485
756	1-[1-(3,5-Dichloro-phenyl)-2,5-dimethyl-1H-pyrrole-3-carbonyl]-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester	554, 556
757	1-(1H-Pyrrolo[3,2-c]pyridin-2-ylmethyl)-4-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)-piperazin-2-one	361
758	4-(3-Phenyl-prop-2-ynyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	345
759	4-[3-(5-Chloro-thiophen-2-yl)-prop-2-ynyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	384

The following compounds are prepared from 3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one using the procedures described above.

Example	Name	m/z [M+H]
760	4-[3-(5-Chloro-thiophen-2-yl)-allyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	431, 433
761	4-(5-Chloro-1H-indol-2-ylmethyl)-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	438, 440
762	4-(5'-Chloro-[2,2']bithiophenyl-5-ylmethyl)-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	487, 489
763	4-(6-Chloro-benzo[b]thiophene-2-carbonyl)-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	469, 471
764	4-[1-(3,5-Dichloro-phenyl)-2,5-dimethyl-1H-pyrrole-3-carbonyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	540, 542
765	4-[3-(4-Chloro-phenyl)-(E)-acryloyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	439, 441
766	(S)-2-Methoxymethyl-3-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	428, 430
767	(S)-4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-3-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	445, 447

EXAMPLE 768. 4-(6-Chloro-benzo[b]thiophene-2-carbonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one.

A. 2-[4-(6-Chloro-benzo[b]thiophene-2-carbonyl)-2-oxopiperazin-1-ylmethyl]-(pyrrolo[3,2-c]pyridin-1-carboxylic acid tert-butyl ester.

The title compound is prepared as described in EXAMPLE 123 using 6-chloro-benzo[b]thiophene-2-carboxylic acid, EXAMPLE 1 and 2-(2-oxopiperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridin-1-carboxylic acid tert-butyl ester EXAMPLE 69. The mixture is stirred overnight, then concentrated to dryness. The residue is diluted with CH_2Cl_2 and washed with saturated sodium bicarbonate and brine. The organic layer is dried over $MgSO_4$, filtered and concentrated in vacuo to give the title compound as a solid. The crude material can be used in the subsequent step without further purification.

B. 4-(6-Chloro-benzo[b]thiophene-2-carbonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one.

Trifluoroacetic acid (0.5 mL) is added dropwise to a solution of 2-[4-(6-chloro-benzo[b]thiophene-2-carbonyl)-2-oxopiperazin-1-ylmethyl]-(pyrrolo[3,2-c]pyridin-1-carboxylic acid tert-butyl ester (0.14 g, 0.27 mmol) in 6 mL CH_2Cl_2 at 0°C. After 1 h, the ice bath is removed and the solution stirred at room temperature for 2 hours. The reaction mixture is concentrated in vacuo. The crude residue is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 100% CH_3CN and the appropriate product fractions are combined and lyophilized to provide the title compound (0.07 g, 0.13 mmol) as a white solid. ESI MS, $[M+H]^+$=425, 427 (Cl pattern).

The following compounds are prepared using starting materials obtained as described in Example 69 using the methods described above.

Example	Name	m/z [M+H]
769	4-[3-(6-Chloro-benzo[b]thiophen-2-yl)-(E)-acryloyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	451, 453
770	4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	405, 407
771	4-[1-(3,5-Dichloro-phenyl)-2,5-dimethyl-1H-pyrrole-3-carbonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	497, 499
772	4-(5'-Chloro-[2,2']bithiophenyl-5-carbonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	457, 459
773	4-(5-Chloro-1H-indole-2-carbonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	364, 366
774	4-[4-(6-Methoxy-pyridin-3-yl)-benzoyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	442
775	4-(4-Pyridin-3-yl-benzoyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	412
776	4-[3-(4-Bromo-thiophen-2-yl)-(E)-acryloyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	446
777	4-[3-(5-Chloro-thiophen-2-yl)-propionyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	403, 405
778	4-[(5-Chloro-3-methyl-benzo[b]thiophen-2-yl)-acetyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	453, 455
779	4-[2-(4-Chloro-phenyl)-2-methyl-propionyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	411, 413

780	4-[3-(3,4-Dichloro-phenyl)-(E)-acryloyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	431, 433
781	4-[(4-Chloro-phenyl)-acetyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	383, 385
782	4-[3-(4-Chloro-phenyl)-(E)-acryloyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	395, 397
783	4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	400, 402

EXAMPLE 784. (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid methyl ester.

A. (±)-4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-5-oxo-piperazine-1,3-dicarboxylic acid 1-allyl ester 3-methyl ester.

To a solution containing (S)-5-oxo-piperazine-1,3-dicarboxylic acid 1-allyl ester 3-methyl ester (0.43 g, 1.77 mmol), EXAMPLE 56, and 2-(benzhydrylidene-amino)-4-bromomethyl-benzonitrile (0.66 g, 1.77 mmol), EXAMPLE 13, in anhydrous DMF (5 mL) at 0°C is added 60% NaH (78 mg, 1.95 mmol). After 30 min, the reaction mixture is warmed to ambient temperature and maintained for 6 hours. The reaction mixture is carefully quenched with water and then diluted with water and diethyl ether. The layers are separated and the organic phase is washed twice with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue is chromatographed on silica gel (2:1 hexane/ethyl acetate to 1:1 hexane/ethyl acetate) to provide 0.37 g (39%) of the title compound as a glassy solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.01-3.22 (m, 2H), 3.58 (m, 2H), 3.73 (s, 3H), 3.86-3.92 (m, 1H), 4.42-4.58 (m, 4H), 5.25 (m, 2H), 5.93 (m, 1H), 6.57 (br s, 1H), 6.85 (d, J = 8.2 Hz, 1 H), 7.17-7.51 (m, 9H), 7.76 (m, 2H) ppm; MS (ion spray): m/z 537 (M+H).

B. (±)-1-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-6-oxo-piperazine-2-carboxylic acid methyl ester.

Tetrakis(triphenylphosphine)palladium(0) (237 mg, 0.2 mmol) is added to a solution containing (±)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-5-oxo-piperazine-1,3-dicarboxylic acid 1-allyl ester 3-methyl ester (1.10 g, 2.05 mmol) and morpholine (894 mg, 10.2 mmol) in CH_2Cl_2 (30 mL). After ~5 min, the reaction mixture is absorbed onto silica gel and chromatographed (CH_2Cl_2 to 10% MeOH/ CH_2Cl_2) to provide 900 mg (97%) of the title compound as a viscous yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.83 (br s, 1H), 2.95 (dd, J = 13.5, 4.3 Hz, 1H), 3.27 (br

d, J = 13.5 Hz, 1H), 3.46-3.72 (m, 4H), 3.73 (s, 3H), 5.40 (d, J = 15.3 Hz, 1H), 6.57 (br s, 1H), 6.83 (dd, J = 8.0, 1.2 Hz, 1H), 7.17-7.50 (m, 9H), 7.75-7.77 (m, 2H) ppm; MS (ion spray): m/z 453 (M+H).

C. (±)-2-{4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-methoxycarbonyl-5-oxo-piperazin-1-ylmethyl}-5-chloro-indole-1-carboxylic acid tert-butyl ester.

To a mixture of (±)-1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-6-oxo-piperazine-2-carboxylic acid methyl ester (630 mg, 1.39 mmol) and K_2CO_3 (380 mg, 2.78 mmol) in anhydrous CH_3CN (5 mL) at 0 °C is added 2-bromomethyl-5-chloro-indole-1-carboxylic acid tert-butyl ester (720 mg, 2.09 mmol), EXAMPLE 21, in CH_3CN (4 mL). The reaction mixture is allowed to warm to ambient temperature then maintained for 16 hours. The reaction mixture is diluted with diethyl ether/water and the layers are separated. The organic phase is washed twice with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue is chromatographed on silica (CH_2Cl_2 to 2% MeOH/ CH_2Cl_2) to provide 550 mg (55%) of the title compound which is used directly in the next reaction without further characterization.

D. (±)-2-[4-(3-Amino-4-cyano-benzyl)-3-methoxycarbonyl-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester.

Partially-purified (±)-2-{4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-methoxycarbonyl-5-oxo-piperazin-1-ylmethyl}-5-chloro-indole-1-carboxylic acid tert-butyl ester (550 mg, 0.76 mmol) is suspended in reagent grade MeOH (20 mL). To the heterogeneous mixture is added 12M HCl (5 drops) and the reaction mixture is maintained at ambient temperature until homogeneous (~30 min). The reaction mixture is partitioned between diethyl ether and water containing excess $NaHCO_3$ (500 mL). The layers are separated and the organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue is chromatographed on silica gel (CH_2Cl_2 to 2% MeOH/ CH_2Cl_2) to provide 400 mg (94%) of the title compound which is used directly in the next reaction. MS (ISP loop): 532 (M+H).

E. (±)-2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-methoxycarbonyl-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester.

A solution containing (±)-2-[4-(3-amino-4-cyano-benzyl)-3-methoxycarbonyl-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester (100 mg, 0.18 mmol), 1,3,5-triazine (146 mg, 1.81 mmol), and glacial HOAc (99 mg, 1.81 mmol) in absolute EtOH (10 mL) is maintained at reflux for 16 hours. A second portion of 1,3,5-triazine (146 mg, 1.81 mmol) and glacial HOAc (99 mg, 1.81 mmol) is added and the reaction mixture is maintained at reflux

for an additional 16 hours. The reaction mixture is concentrated in vacuo and the crude product is diluted with water/CH_3CN and purified by reverse-phase HPLC [Buffer A: water w/0.1% TFA; Buffer B: CH_3CN w/0.1% TFA; Gradient: 0%B to 60%B over 30 min] to provide 26 mg (20%) of the title compound as a white solid which is used directly in the next reaction without further characterization.

F. (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid methyl ester.

To a solution containing (±)-2-[4-(4-amino-quinazolin-7-ylmethyl)-3-methoxycarbonyl-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester (26 mg, 0.03 mmol) in CH_2Cl_2 (4 mL) is added trifluoroacetic acid (1mL) at ambient temperature. After 4 h, the reaction mixture is concentrated in vacuo and then dissolved in water/CH_3CN and purified by reverse-phase HPLC [Buffer A: water w/0.1% TFA; Buffer B: CH_3CN w/0.1% TFA; Gradient: 0%B to 60%B over 30 min] to provide 10 mg (47%) of the title compound as a white solid. ^1H NMR (300 MHz, d_6-DMSO) δ 2.62 (m, 1H), 3.05-3.51 (m, 4H), 3.59 (s, 3H), 3.81 (d, J = 14.0 Hz, 1H), 4.26 (m, 1H), 4.69 (ABq, Δ_{AB} = 310 Hz, J_{AB} = 16.4 Hz, 2H), 6.26 (s, 1H), 7.02 (dd, J = 8.6, 2.0 Hz, 1H), 7.31 (d, J = 8.6 Hz, 1H), 7.49 (d, J = 2.0 Hz, 1H), 7.52 (s, 1H), 7.61 (d, J = 8.7 Hz, 1H), 8.30 (d, J = 8.6 Hz, 1H), 8.47 (s, 1H), 8.77 (s, 1H), 9.69 (br s, 2H), 11.17 (s, 1H) ppm; MS (ion spray): m/z 479 (M+H).

EXAMPLE 785. (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid.

A. (±)-1-(3-Amino-4-cyano-benzyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid.

LiOH monohydrate (380 mg, 9.06 mmol) is added at ambient temperature to a solution containing (±)-2-[4-(3-amino-4-cyano-benzyl)-3-methoxycarbonyl-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester (1.0 g, 1.81 mmol), EXAMPLE 784, Part E, in 1:1:1 THF/MeOH/water (30 mL). After 16 h, HOAc (0.5 mL) is added and the reaction mixture is concentrated in vacuo. The residue is dissolved in CH_3CN/water and purified by reverse-phase HPLC [Buffer A: water w/0.1% TFA; Buffer B: CH_3CN w/0.1% TFA; Gradient: 0%B to 60%B over 30 min] to provide 378 mg (48%) of the title compound as a white solid. ^1H NMR (300 MHz, d_6-DMSO) δ 3.03 (m, 1H), 3.48 (m, 1H), 3.51 (ABq, Δ_{AB} = 69.2 Hz, J_{AB} = 16.4 Hz, 2H), 3.78 (d, J = 15.9 Hz, 1H), 4.05-4.09 (m, 2H), 5.04 (d, J = 15.9 Hz, 1H), 6.41 (m, 2H), 6.58

(s, 1H), 7.04 (dd, J = 8.6, 2.0 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 8.6 Hz, 1H), 7.51, d, J = 2.0 Hz, 1H) ppm; MS (ISP loop): m/z 438 (M+H).

B. (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid

A solution containing (±)-1-(3-amino-4-cyano-benzyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid (200 mg, 0.30 mmol), 1,3,5-triazine (244 mg, 3.00 mmol), and glacial HOAc (180 mg, 3.00 mmol) in absolute EtOH (20 mL) is maintained at reflux for 16 hours. The reaction mixture is cooled to ambient temperature and the solid is collected on a Buchner funnel and washed with EtOH followed by diethyl ether. Oven-drying in vacuo provided 13 mg (76%) of the title compound as an off-white solid. ^{1}H NMR (300 MHz, d_6-DMSO) δ 2.63 (m, 1H), 3.06 (d, J = 16.4 Hz, 1H), 3.24-3.42 (m, 4H), 3.68 (ABq, Δ_{AB} = 34.5 Hz, J_{AB} = 14.1 Hz, 2H), 3.96 (m, 1H), 4.63 (ABq, Δ_{AB} = 400 Hz, J_{AB} = 15.8 Hz, 2H), 6.27 (s, 1H), 6.99 (dd, J = 8.6, 2.0 Hz, 1H), 7.29 (d, J = 8.5 Hz, 2H), 7.40 (s, 1H), 7.46 (s, 1H), 7.69 (br s, 2H), 8.10 (d, J = 8.5 Hz, 1H), 8.32 (s, 1H), 11.20 (s, 1H) ppm; MS (ion spray): m/z 465 (M+H).

EXAMPLE 786. (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid methylamide

To a solution containing (±)-1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid (25 mg, 0.03 mmol), EXAMPLE 785, and N-methylmorpholine (36 mg, 0.36 mmol) in anhydrous DMF (1 mL) is added methylamine hydrochloride (10 mg, 0.14 mmol) followed by HATU (40 mg, 0.10 mmol) at ambient temperature. After 3 h, the solvent is removed under high vacuum and the residue is dissolved in CH_3CN/water and purified by reverse-phase HPLC [Buffer A: water w/0.1% TFA; Buffer B: CH_3CN w/0.1% TFA; Gradient: 0%B to 60%B over 30 min] to provide 22 mg (88%) of the title compound as a white solid. ^{1}H NMR (300 MHz, d_6-DMSO) δ 2.57 (d, J = 4.4 Hz, 3H), 2.70 (m, 1H), 3.0 (m, 1H), 3.66 (d, J = 14.2 Hz, 1H), 3.77 (d, J = 14.2 Hz, 1H), 3.85 (m, 1H), 4.03 (d, J = 16.3 Hz, 1H), 5.18 (d, J = 16.3 Hz, 1H), 6.28 (s, 1H), 7.02 (dd, J = 8.5, 2.0 Hz, 1H), 7.31 (d, J = 8.5 Hz, 1H), 7.49 (d, J = 2.0 Hz, 1H), 7.51 (s, 1H), 7.58 (d, J = 8.6 Hz, 1H), 7.97 (m, 1H), 8.31 (d, J = 8.6 Hz, 1H), 8.79 (s, 1H), 9.72 (br s, 2H), 11.18 (s, 1H) ppm; MS (ISP loop): m/z 478 (M+H).

Table 1: Amide Analogs Derived From C-6 Carboxylic Acid.

Example	Name	m/z

		[M+H]
787	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid ethylamide	492
788	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid dimethylamide	492
789	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid benzylamide	554
790	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid (2-hydroxy-ethyl)-amide	508
791	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid bis-(2-hydroxy-ethyl)-amide	552
792	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-(morpholine-4-carbonyl)-piperazin-2-one	534
793	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid methylcarbamoylmethyl-amide	535

The following compounds are prepared using the procedures described above.

Example	Name	m/z [M+H]
794	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-oxo-piperazine-2-carboxylic acid	458
795	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-oxo-piperazine-2-carboxylic acid methyl ester	472
796	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-oxo-piperazine-2-carboxylic acid amide	457
797	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-oxo-piperazine-2-carboxylic acid ethylamide	458
798	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-(4-methyl-piperazine-1-carbonyl)-piperazin-2-one	540

EXAMPLE 799. (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester.

A solution containing (±)-1-(3-amino-4-cyano-benzyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester (42 mg, 0.08 mmol), EXAMPLE 99, 1,3,5-triazine (40 mg, 0.48 mmol), and glacial HOAc (30 mg, 0.48 mmol) in absolute EtOH (1 mL) is maintained at reflux for 16 hours. The reaction mixture is concentrated and then dissolved in water/CH_3CN and purified by reverse-phase HPLC [Buffer A: water w/ 0.1% TFA;

Buffer B: CH3CN w/ 0.1% TFA; Gradient: 0% B to 60% B over 30 min] to provide 17 mg (32%) of the title compound as a white solid.

^{1}H NMR (300 MHz, d_6-DMSO) δ 3.47 (m, 1H), 3.67 (s, 3H), 3.71 (d, J = 16.1 Hz, 1H), 4.00 (d, J = 16.5 Hz, 1H), 4.05 (m, 1H), 4.52 (m, 1H), 4.72 (ABq, Δ_{AB} = 248 Hz, J_{AB} = 16.5 Hz, 2H), 7.57 (m, 2H), 8.05 (d, J = 8.6 Hz, 1H), 8.20 (s, 1H), 8.23 (d, J = 8.5 Hz, 1H), 8.35 (d, J = 1.9 Hz, 1H), 8.49 (s, 1H), 8.72 (s, 1H), 9.57 (br s, 2H) ppm; MS (ion spray): m/z 546 (M+H).

EXAMPLE 800. (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid.

Water (1 mL) is added to a solution containing (±)-1-(4-amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester (20 mg, 0.03 mmol), EXAMPLE 799, in a 1:1 mixture of THF/MeOH (2 mL). At ambient temperature, LiOH monohydrate (15 mg, 0.35 mmol) is then added. After 16 h, the reaction mixture is diluted with water and purified by reverse-phase HPLC [Buffer A: water w/ 0.1% TFA; Buffer B: CH3CN w/ 0.1% TFA; Gradient: 0% B to 60% B over 30 min] to provide 12 mg (63%) of the title compound as a white solid.

^{1}H NMR (300 MHz, d_6-DMSO) δ 3.69 (d, J = 16.0 Hz, 1H), 3.97 (d, J = 16.0 Hz, 1H), 4.08 (d, J = 11.7 Hz, 1H), 4.18 (d, J =16.2 Hz, 1H), 4.31 (d, J = 2.7 Hz, 1H), 5.20 (d, J =16.2 Hz, 1H), 7.47 (d, J = 8.7 Hz, 1H), 7.52 (s, 1H), 7.58 (dd, J = 8.6, 1.9 Hz, 1H), 8.06 (d, J = 8.7 Hz, 1H), 8.16 (d, J = 8.6 Hz, 1H), 8.19 (s, 1H), 8.34 (d, J = 1.9 Hz, 1H), 8.54 (s, 1H), 8.77 (br s, 1H) ppm; MS (ion spray): m/z 532 (M+H).

EXAMPLE 801. (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid amide

To a mixture containing (±)-1-(4-amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid (45 mg, 0.08 mmol), EXAMPLE 800, N-methylmorpholine (18 mg, 0.18 mmol), and HATU (35 mg, 0.09 mmol) in anhydrous DMF (1 mL) is added NH_3 (7N in MeOH, 2 drops, approx. 0.5 mmol). The heterogeneous mixture is stirred 16 h at ambient temprature and then concentrated to dryness. The residue is dissolved in water and purified by reverse-phase HPLC [Buffer A: water w/ 0.1% TFA; Buffer B: CH3CN w/ 0.1% TFA; Gradient: 0% B to 60% B over 30 min] to provide 25 mg (46%) of the title compound as a white solid. ^{1}H NMR (300 MHz, d_6-DMSO) δ 3.63 (d, J = 16.0 Hz, 1H), 4.01 (m, 4H), 5.17 (d, J = 16.6 Hz, 1H), 7.58 (m, 3H), 8.08 (d, J = 8.6 Hz, 1H), 8.17 (s, 1H), 8.26 (d, J = 8.6 Hz, 1H), 8.34 (d, J = 1.9 Hz, 1H), 8.74 (s, 1H), 9.63 (br s, 2H) ppm; MS (ISP loop): m/z 531 (M+H).

The following compounds are prepared using the procedures described above.

Example	Name	m/z [M+H]
802	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid ethyl ester	560
803	(+/-)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid	531
804	(+/-)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methylamide	544
805	(+/-)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid ethylamide	558
806	(+/-)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid dimethylamide	558
807	(+/-)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-(morpholine-4-carbonyl)-piperazin-2-one	600

EXAMPLE 808. (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid methyl ester.

A. (±)-1-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid methyl ester.

To a solution containing (±)-1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-6-oxo-piperazine-2-carboxylic acid methyl ester (1.17 g, 2.6 mmol), EXAMPLE 784, Part B, 5-chlorothiophen-2-yloxyacetic acid (0.5 g, 2.6 mmol), EXAMPLE 24,and N-methylmorpholine (0.58 g, 5.72 mmol) in anhydrous DMF (10 mL) is added HATU (1.09 g, 2.86 mmol) at ambient temperature. After 1.5 h, the reaction mixture is diluted with CH_2Cl_2 (100 mL) and aqueous $NaHCO_3$ (100 mL) and the layers are separated. The aqueous phase is washed four times with CH_2Cl_2 (100 mL) and the combined organic phase is washed once with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude amide is purified by flash silica gel chromatography (hexane/EtOAc, 4:1 to 1:2) to afford 1.5 g of the title compound which is used directly in the next reaction. ^1H NMR (300 MHz, $CDCl_3$, ~2:1 mixture of rotomers) major rotomer: δ 3.55 (d, J = 15.2 Hz, 1H), 3.60 (m, 1H), 3.69 (m, 5H), 4.37 (d, J = 17.7 Hz, 1H), 4.62 (m, 2H), 4.79 (d, J = 13.3 Hz, 1H), 5.35 (d, J = 15.2 Hz, 1H), 6.05 (d, J = 3.9 Hz, 1H), 6.52 (m. 2H), 6.84 (d, J = 8.1 Hz, 1H), 7.18-7.49 (m, 11H), 7.76 (m, 1H) ppm; MS (ISP loop): m/z 627 (M+H).

B. (±)-1-(3-Amino-4-cyano-benzyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid methyl ester.

Concentrated HCl (12M, 0.5 mL) is added at 0 °C to a solution containing (±)-1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid methyl ester (1.5 g, 2.39 mmol) in 4:1 MeOH/THF (25 mL). After 1.5 h, the reaction mixture is concentrated to dryness and then partitioned between a 1:1 mixture of EtOAc/aqueous $NaHCO_3$ (200 mL) and the layers are separated. The aqueous phase is extracted with EtOAc and then the combined organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue is chromatographed on silica gel (hexane/EtOAc, 4:1 to 1:2) to provide 934 mg (84%, two steps) of the title compound. ^1H NMR (300 MHz, $CDCl_3$, ~2:1 mixture of rotomers) selected peaks: δ 3.16 (app. dd, J 14.0, 3.8 Hz, 1H), 3.68 (s, 3H), 3.96 (app. dd, J = 3.8, 2.0 Hz, 1H), 4.17 (d, J = 17.7 Hz, 1H), 4.45 (br s, 2H), 4.62 (m, 2H), 4.87 (d, J = 14.1 Hz, 1H), 5.21 (d, J = 15.1 Hz, 1H), 6.07 (m, 1H), 6.51 (d, J = 3.8 Hz, 1H), 6.57 (d, J = 7.9 Hz, 1H), 6.62 (br s, 1H), 7.35 (d, J = 7.9 Hz, 1H) ppm; MS (ISP loop): m/z 463 (M+H).

C. (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid methyl ester.

A solution containing (±)-1-(3-amino-4-cyano-benzyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid methyl ester (110 mg, 0.25 mmol), 1,3,5-triazine (207 mg, 2.55 mmol), and glacial HOAc (157 mg, 2.55 mmol) in absolute EtOH (5 mL) is maintained at reflux for 16 hours. The reaction mixture is concentrated to dryness and then purified by reverse-phase HPLC [Buffer A: water w/ 0.1% TFA; Buffer B: CH3CN w/ 0.1% TFA; Gradient: 0% B to 60% B over 30 min] to provide 50 mg (32%) of the title compound as a white solid. ^1H NMR (300 MHz, d_6-DMSO) δ 3.34-3.89 (m, 2H), 3.60 (s, 3H), 4.14-4.54 (m, 3H), 4.64 (br d, J = 14.4 Hz, 1H), 4.78-5.11 (m, 3H), 6.19 (d, J = 4.1 Hz, 1H), 6.73 (d, J = 4.1 Hz, 1H), 7.64 (s, 1H), 7.65 (d, J = 9.0 Hz, 1H), 8.34 (d, J = 9.0 Hz, 1H), 8.79 (s, 1H), 9.71 (br s, 2H) ppm; MS (ion spray): m/z 490 (M+H).

EXAMPLE 809. (±)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid methylamide.

Water (1 mL) is added to a solution containing (±)-1-(4-amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid methyl ester (20 mg, 0.03 mmol), EXAMPLE 808, in a 1:1 mixture of THF/MeOH (2 mL). At ambient temperature,

LiOH monohydrate (3 mg, 0.07 mmol) is then added. After 16 h, the reaction mixture is diluted with water and purified by reverse-phase HPLC [Buffer A: water w/ 0.1% TFA; Buffer B: CH3CN w/ 0.1% TFA; Gradient: 0% B to 60% B over 30 min] to provide 25 mg (>100 %) of the associated acid as a white solid after lyophilization which is used directly in the next reaction.

To a mixture containing (+/-)-1-(4-amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid (12 mg, 0.02 mmol), N-methylmorpholine (19 mg, 0.19 mmol), and HATU (22 mg, 0.05 mmol) in anhydrous DMF (1 mL) is added $MeNH_2$ hydrochloride (5 mg, 0.19 mmol). The reaction mixture is stirred 1 h at ambient temperature and then concentrated to dryness. The residue is dissolved in water and purified by reverse-phase HPLC [Buffer A: water w/ 0.1% TFA; Buffer B: CH3CN w/ 0.1% TFA; Gradient: 0% B to 60% B over 30 min] to provide 7 mg (58%) of the title compound as a white solid. ^1H NMR (300 MHz, d_6-DMSO) mixture of rotamers: δ 2.51 (m, 3H), 4.07-4.54 (m, 6H), 4.87 (m, 2H), 5.10 (m, 1H), 6.18 (m, 1H), 6.74 (m, 1H), 7.62 (m, 2H), 8.06 (br s, 1H), 8.32 (br d, J = 8.8 Hz, 1H), 8.78 (s, 1H), 9.61 (br s, 2H) ppm; MS (ISP loop): 489 (M+H).

The following compound is prepared using the procedures described above.

Example	Name	m/z [M+H]
810	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid ethylamide	503

EXAMPLE 811. (+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid.

Water (0.5 mL) is added to a solution containing (±)-1-(3-amino-4-cyano-benzyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid methyl ester (35 mg, 0.08 mmol), EXAMPLE 808, Part B, in a 1:1 mixture of THF/MeOH (1 mL). At ambient temperature, LiOH monohydrate (4 mg, 0.10 mmol) is then added. After 16 h, an additional portion of LiOH monohydrate (4 mg, 0.10 mmol) is added and the reaction mixture is stirred for another 2 h then diluted with water and purified by reverse-phase HPLC [Buffer A: water w/ 0.1% TFA; Buffer B: CH3CN w/ 0.1% TFA; Gradient: 0% B to 60% B over 30 min] to provide 40 mg (95%) of the associated acid as a white solid after lyophilization which is used directly in the next reaction. MS (ISP loop): m/z 449 (M+H).

A solution containing (+/-)-1-(3-amino-4-cyano-benzyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid (20 mg, 0.03 mmol), 1,3,5-triazine (28 mg, 0.34 mmol), and glacial HOAc (20 mg, 0.34 mmol) in absolute EtOH (6 mL) is maintained at reflux for 16 hours. The reaction mixture is concentrated to dryness and then purified by reverse-

phase HPLC [Buffer A: water w/ 0.1% TFA; Buffer B: CH3CN w/ 0.1% TFA; Gradient: 0% B to 60% B over 30 min] to provide 15 mg (75%) of the title compound as a white solid. ^{1}H NMR (300 MHz, d_6-DMSO) δ 3.75-4.38 (m, 5H), 4.67 (d, J = 14.8 Hz, 1H), 4.79 (d, J = 15.3 Hz, 1H), 4.95 (m, 1H), 5.09 (br d, J = 16.0 Hz, 1H), 6.18 (m, 1H), 6.71 (m, 1H), 7.64 (m, 2H), 8.31 (d, J = 8.5 Hz, 1H), 8.75 (s, 1H), 9.64 (br s, 2H) ppm; MS (ISP loop): m/z 476 (M+H).

EXAMPLE 812. 4-Prop-2-ynyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

A. 2-(2-Oxo-4-prop-2-ynyl-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

A solution containing 2-(2-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (4.3 g, 13.0 mmol), EXAMPLE 69, in CH_3CN (250 mL) is cooled to 0°C. Potassium carbonate (1.98 g, 14.3 mmol) is added to the reaction mixture followed by propargyl bromide (1.55g, 13.0 mmol). The mixture is slowly warmed to ambient temperature and maintained until complete consumption of starting material is observed by TLC (approx. 8 h). The mixture is concentrated to dryness and then partitioned between aqueous $NaHCO_3$ (200 mL) and CH_2Cl_2 (200 mL) and the layers are separated. The aqueous phase is extracted twice with CH_2Cl_2 (100 mL) and the combined organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue is purified by flash silica gel chromatography (CH_2Cl_2 to 5% MeOH/CH_2Cl_2) to provide 3.38 g (70%) of the title compound as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.69 (s, 9H), 2.34 (t, J = 2.4 Hz, 1H), 2.89 (m, 2H), 3.42 (s, 2H), 3.45 (d, J = 2.4 Hz, 2H), 3.52 (m, 2H), 4.95 (d, J = 1.4 Hz, 2H), 6.42 (br s, 1H), 7.88 (dd, J = 5.8, 0.8 Hz, 1H), 8.41 (d, J = 5.8 Hz, 1H), 8.78 (d, J = 0.8 Hz, 1H) ppm; MS (EI): m/z 368 (M+).

B. 4-Prop-2-ynyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

To a solution containing 2-(2-oxo-4-prop-2-ynyl-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (1.3 g, 3.53 mmol) in CH_2Cl_2 (100 mL) is added TFA (20 mL) at 0 °C. After 6 h, the reaction mixture is concentrated to dryness and then partitioned between aqueous $NaHCO_3$ (500 mL) and CH_2Cl_2 (200 mL) and the layers are separated. The aqueous phase is extracted four times with CH_2Cl_2 (100 mL) and the combined organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue is purified by flash silica gel chromatography (CH_2Cl_2 to 10% MeOH/CH_2Cl_2) to provide 616 mg (65%) of the title compound as a pale yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.27 (app t, J = 2.4 Hz, 1H), 2.76 (m, 2H), 3.33 (s, 2H), 3.83 (d, J = 2.4 Hz, 2H), 3.45 (m, 2H), 4.57 (s, 2H), 6.47 (s, 1H), 7.23 (d, J = 5.7 Hz, 1H), 8.28 (d, J = 5.7 Hz, 1H), 8.85 (d, J = 0.9 Hz, 1H), 9.34 (br s, 1H) ppm; MS (EI): m/z 268 (M+).

EXAMPLE 813. 1,4-Bis-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

A. 2-{4-[3-(4-tert-Butoxycarbonylamino-pyridin-3-yl)-prop-2-ynyl]-2-oxo-piperazin-1-ylmethyl}-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

A solution containing 2-(2-oxo-4-prop-2-ynyl-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (100 mg, 0.27 mmol), EXAMPLE 812, (3-iodo-pyridin-4-yl)-carbamic acid tert-butyl ester (87 mg, 0.27 mmol), EXAMPLE 69, Part B, Et_3N (110 mg, 1.08 mmol), $(Ph_3P)_4PdCl_2$ (10 mg, 0.013 mmol), and CuI (1 mg, 0.008 mmol) in anhydrous DMF (5 mL) is stirred at ambient temperature. After 5 h, the reaction mixture is diluted with EtOAc (50 mL) and water (50 mL) and the layers are separated. The aqueous layer is extracted twice with EtOAc (25 mL) and the combined organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue is purified by flash silica gel chromatography (CH_2Cl_2 to 10% MeOH CH_2Cl_2) to provide 77 mg (51%) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ~2:1mixture of rotamers) major rotamer: δ 1.53 (s, 9H), 1.69 (s, 9H), 2.98 (m, 2H), 3.49 (s, 2H), 3.56 (m, 2H), 3.78 (s, 2H), 4.98 (s, 2H), 6.43 (s, 1H), 7.89 (m, 1H), 8.09 (m, 2H), 8.34 (m, 1H), 8.41 (m, 1H), 8.75 (m, 1H) ppm; MS (ISP loop): m/z 561 (M+H).

B. 2-[4-(1-tert-Butoxycarbonyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

1,8-Diazabicyclo[5.4.0]undec-7-ene (42 mg, 0.27 mmol) is added to a suspension containing 2-{4-[3-(4-tert-butoxycarbonylamino-pyridin-3-yl)-prop-2-ynyl]-2-oxo-piperazin-1-ylmethyl}-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (77 mg, 0.14 mmol) in anhydrous CH_3CN (10 mL) and the mixture is warmed to 50 °C. After 4 h, the reaction mixture is concentrated to dryness and the residue is partitioned between CH_2Cl_2 (50 mL) and water (50 mL) and the layers are separated. The aqueous layer is extracted twice with CH_2Cl_2 (25 mL) and the combined organic phase is washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to provide 85 mg of the title compound as a crude solid which is used directly without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68 (s, 9H), 1.70 (s, 9H), 2.91 (m, 2H), 3.41 (s, 2H), 3.49 (m, 2H), 4.26 (s, 2H), 4.95 (d, J = 1.1 Hz, 2H), 6.39 (d, J = 0.7 Hz,

1H), 6.68 (d, J = 0.7 Hz, 1H), 7.86 (m, 1H), 8.41 (m, 1H), 8.76 (br s, 1H), 8.82 (br s, 1H) ppm; MS (EI): m/z 561 (M+H).

C. 1,4-Bis-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

To a solution containing 2-[4-(1-tert-Butoxycarbonyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (85 mg, 0.14mmol) in CH_2Cl_2 (5 mL) is added TFA (1 mL) at 0 °C and the solution is allowed to slowly warm to ambient temperature. After 16 h, the reaction mixture is concentrated to dryness, diluted with water and purified by reverse-phase HPLC [Buffer A: water w/ 0.1% TFA; Buffer B: CH3CN w/ 0.1% TFA; Gradient: 0% B to 45% B over 30 min] to provide 35 mg (36%, two steps) of the title compound as a pale yellow, lyophilized solid.
^{1}H NMR (300 MHz, d_6-DMSO) δ 2.80 (m, 2H), 3.25 (s, 2H), 3.37 (m, 2H), 3.93 (s, 2H), 4.76 (s, 2H), 6.88 (s, 1H), 6.94 (s, 1H), 7.85 (d, J = 6.6 Hz, 1H), 7.89 (d, J = 6.6 Hz, 1H), 8.37 (d, J = 6.7 Hz, 1H), 8.38 (d, J = 6.7 Hz, 1H), 9.17 (s, 1H), 9.19 (s, 1H), 12.80 (s, 1H), 12.96 (s, 1H), 14.91 (br s, 2H) ppm; MS (ion spray): m/z 361 (M+H). $C_{23}H_{25}ClN_4OS$ MS m/z: 441,443.

EXAMPLE 814. 2-Amino-4-[4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperidin-1-ylmethyl]-benzonitrile.

A. {1-[3-Benzhydrylidene-amino)-4-cyano-benzyl]-2-oxo-piperidin-4-yl}-acetic acid ethyl ester:

Sodium hydride (140 mg, 3.51 mmol) is added to a cooled solution of (2-oxo-piperidin-4-yl)-acetic acid ethyl ester (500 mg, 2.70 mmol) in 10 mL of THF. After stirring for forty five minutes, 2-(benzhydrylidene-amino)-4-bromomethyl-benzonitrile (1.43 g, 3.82 mmol), EXAMPLE 13, is added, and the reaction is left to stir overnight. THF is removed, and the residue is taken up in 250 mL of ethyl acetate. Excess sodium hydride is quenched with 5 mL of water, and normal aqueous work-up followed. The crude product is chromatographed on silica gel (50% EtOAc/Hexane) to give{1-[3-benzhydrylidene-amino)-4-cyano-benzyl]-2-oxo-piperidin-4-yl}-acetic acid ethyl ester (732 mg, 57%)as a light yellow solid. $C_{30}H_{29}N_3O_3$ MS m/z: 480, 482. Anal cald. for $C_{30}H_{29}N_3O_3$: C,75.13; H, 6.09; N, 8.76. Found C, 73.01; H, 6.02; N, 8.46.

B. {1-[3-Benzhydrylidene-amino)-4-cyano-benzyl]-2-oxo-piperidin-4-yl}-acetic acid.

To a solution of {1-[3-benzhydrylidene-amino)-4-cyano-benzyl]-2-oxo-piperidin-4-yl}-acetic acid ethyl ester (732 mg, 1.53 mmol) in 5 mL of THF is added 1N sodium hydroxide (1.53 ml, 1.53 mmol). After stirring for four hours, the THF is removed and EtOAc (500 mL) is added.

The reaction mixture is acidified to a pH of 6 and normal aqueous work-up followed. The desired carboxylic acid (571 mg, 83% yield) is isolated as a white solid.

C. N-(2-Amino-5-chloro-phenyl)-2-{1-[3-(benzhydrylidene-amino)-4-cyano-benyl]-2-oxo-piperidin-4-yl}-acetamide.

To a slurry of the {1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-2-oxo-piperidin-4-yl}-acetic acid (190 mg, 0.422 mmol) in THF (5 mL) and methylene chloride (3 mL) is added triethylamine (0.09 ml, 0.633 mmol). The solution is cooled to 0 °C , and 1M isopropyl chloroformate in toluene (0.422 mL, 0.422 mmol) is added. The homogenous mixture is allowed to warm to room temperature, and 4-chloro-1,2-phenylene-diamine (150 mg, 1.06 mmol) is added. The reaction is stirred at room temperature overnight. The volatile solvents are removed, and the resulting residue is chromatographed (SiO_2, 5%MeOH/EtOAc) to give N-(2-amino-5-chloro-phenyl)-2-{1-[3-(benzhydrylidene-amino)-4-cyano-benyl]-2-oxo-piperidin-4-yl}-acetamide (200 mg, 82% yield). $C_{34}H_{30}ClN_5O_2$ MS m/z: 576, 578.

D. 2-(Benzhydrylidene-amino)-4-[4-(6-cloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperidin-1-ylmethyl}-benzonitrile.

The acetamide (200 mg, 0.35 mmol) is dissolved in 2 mL of acetic acid and refluxed for three hours. The acetic acid is removed, and the residue taken up in ethyl acetate and washed with saturated sodium bicarbonate. Concentration of the solvent afforded 2-(benzhydrylidene-amino)-4-[4-(6-cloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperidin-1-ylmethyl}-benzonitrile (200 mg, 100% yield) which is used without further purification. $C_{34}H_{28}ClN_5O_5$ MS m/z:+ 558, 560.

E. 2-Amino-4-[4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperidin-1-ylmethyl]-benzonitrile hydrochloric acid salt

The above benzonitrile (220 mg, 0.36 mmol) is dissolved in 5 ml of methanol. Hydrochloric acid is bubbled into the ice-cooled methanol solution followed by three drops of water. After stirring at room temperature for one hour, the MeOH is removed. The resulting white solid is titurated with EtOAc. After drying under high vacuum, 2-amino-4-[4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperidin-1-ylmethyl]-benzonitrile hydrochloric acid salt (145.6 mg, 87% yield) is obtained as a white solid. $C_{21}H_{20}ClN_5O$: MS m/z: 394,396.

EXAMPLE 815. 4-[4-(6-Chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperidin-1-ylmethyl]-benzamidine

Hydrochloric acid is bubbled into an ice cooled solution of 4-[4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperidin-1-ylmethyl]-benzonitrile (127 mg, 0.336 mmol) in 10 mL of methanol. The solution also contained 3Å molecular sieves. The reaction is stored at -30 for forty-eight hours. The methanol is condensed on the rotovap. Fresh methanol (15 mL) is added followed by a stream of ammonia gas. The reaction is heated to reflux for two and half hours. The reaction mixture is filtered at room temperature. Methanol is removed from the mother liquor. The resulting residue is purified by reverse phase HPLC (0-50 % ACN/H_2O). The product is isolated as a white solid with a melting point of 105-110 °C . $C_{21}H_{22}ClN_5O$ MS m/z: 396,398. Anal. cald. for $C_{21}H_{22}ClN_5O \cdot 2C_2HF_3O_2$: C, 48.13; H, 3.88; N,11.22. Found: C, 45.05; H, 3.52; N, 9.89.

EXAMPLE 816. 1-(4-Amino-quinazolin-7-ylmethly)-4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-piperidin-2-one.

To a solution of 2-Amino-4-[4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperidin-1-ylmethyl]-benzonitrile hydrochloric acid salt (143 mg, 0.308 mmol), EXAMPLE 814, Part E, in 2 mL of ethanol is added triethylamine (0.05 mL, 0.366 mmol), glacial acetic acid (0.02mL, 0.366 mmol) and triazine (15 mg, 0.183 mmol). The resulting mixture is refluxed overnight. The volatile solvents are removed on the rotovap, and the residue is purified by reverse phase HPLC (0 - 50% Acetonitrile/H_2O). The desired product (110 mg, 55% yield) is isolated as a white powder with a melting point of 128-132 °C . $C_{22}H_{21}ClN_6O$ MS m/z: 421, 423. Anal. calcd. for $C_{22}H_{21}ClN_6O$: C, 48.12; H, 3.57; N, 12.95. Found: C, 45.79; H, 3.68; N, 11.94. H NMR (CD_3OD) δ: 8.67 (s, 1H); 8.31 (d, 1H, J = 4.0 Hz); 7.83-7.55 (m, 5H); 4.93-4.73 (m, 2H); 3.48-3.42 (m, 2H); 3.31-3.21 (m, 2H); 2.71-2.58 (m, 2H); 2.43-2.33 (m, 1H); 2.07- 2.01 (m, 1H); 1.82 - 1.69 (m, 1H).

EXAMPLE 817. 4-(6-Chloro-1H-benzoimidazol-2-ylmethyl)-1-(2,4-diamino-quinazolin-7-ylmethyl)-piperidin-2-one

2-Amino-4-[4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperidin-1-ylmethyl]-benzonitrile hydrochloric acid salt (70 mg, 0.15 mmol), EXAMPLE 814, Part E, pyridine (1.0 mL) and freshly made chloroformamide hydrochloride (150 mg, 1.33 mmol) are placed in a sealed tube and heated to 200 °C . The resulting mixture is heated for twenty four hours. The crude reaction mixture is directly purified by reverse phase HPLC (0-50% ACN/H_2O). The product (53 mg, 45% yield) is isolated as a tanish solid. $C_{22}H_{22}ClN_7O$ MS m/z: 436,438. Anal. calcd. for $C_{22}H_{22}ClN_7O$: C, 43.23; H, 3.24; N, 12.60. Found: C, 43.16; H, 3.44; N, 13.40.

EXAMPLE 818. 1-(4-Amino-2-methyl-quinazolin-7-ylmethly)-4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-piperidin-2-one.

A stream of hydrogen chloride gas is bubbled intermittently through an ice-cold mixture of 2-amino-4-[4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperidin-1-ylmethyl]-benzonitrile hydrochloric acid salt (57 mg, 0.123 mmol), EXAMPLE 814, Part E, and acetonitrile (0.03 mL, 0.93 mmol) in 1.5 mL of dioxane for six hours. The dioxane is removed; the residue is purified by reverse phase HPLC (0-40 % ACN/H_2O). The desired product (9.5 mg, 12% yield) is isolated as a clear wax. $C_{23}H_{23}ClN_6O$ MS m/z : 435, 437.

The following compounds are prepared using the methods described above.

Example	Name	m/z [M+H]
819	(3S, 5R)-4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-3,5-dimethyl-2-oxo-piperazin-1-ylmethyl]-benzamidine	441, 443
820	(3S,5S)-4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-3,5-dimethyl-2-oxo-piperazin-1-ylmethyl]-benzamidine	441, 443
821	4-{4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-3,5-dimethyl-2-oxo-piperazin-1-ylmethyl}-benzamidine	431, 433
822	(3R,5S)-4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-3,5-dimethyl-2-oxo-piperazin-1-ylmethyl]-benzamidine	441, 443

EXAMPLE 823. 2-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-yl]-N-[2-(3H-imidazol-4-yl)-ethyl]acetamide.

A. 4-tert-Butoxycarbonylmethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

To a solution of 3-oxopiperazine-1-carboxylic acid benzyl ester (4.68g, 20mmol) in 20 mL of DMF at) 0°C is added sodium hydride (60%, 880 mg, 22 mmol). The suspension is stirred at ambient temperature for one t-butyl bromoacetate (4.68 g, 24 mmol) is added. The resulting mixture is stirred at ambient temperature overnight. After dilution with ethyl acetate (200 mL), the mixture is washed with brine (3 x 50 mL). The crude residue obtained from concentration of the organic phase is chromatographied on silica gel (30% ethyl acetate/Hexane) to give 5.57 g (80%) of 4-tert-butoxycarbonylmethyl-3-oxopiperazine-1-carboxylic acid benzyl ester as a white solid.

B. (2-Oxo-piperazin-1-yl)acetic acid tert-butyl ester.

4-tert-Butoxycarbonylmethyl-3-oxopiperazine-1-carboxylic acid benzyl ester (2.0g, 5.75 mmol) is dissolved in 20 mL of methanol and 2 mL of acetic acid. Palladium (5%) on carbon (100 mg) is added, and the reaction mixture is stirred in an atmosphere of hydrogen overnight. The mixture is filtered and concentrated. Ethyl acetate is added, and the mixture is neutralized to pH 7 using 1N NaOH. The organic layer is concentrated to give (2-oxo-piperazin-1-yl)acetic acid tert-butyl ester (1.22g).

C. [4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazine-1-yl]acetic acid tert-butyl ester.

To a solution of (2-oxo-piperazin-1-yl)acetic acid tert-butyl ester (1.22 g, 5.7 mmol) in 10 ml of methylene chloride is added triethylamine (1.2 mL, 8.55 mmol) and 6-chlorobenzothiophenesulfonyl chloride (1.52 g, 5.7 mmol). The reaction mixture is stirred overnight at ambient temperature. Flash column chromatography (50 % ethyl acetate / hexane) affords 2.3 g (92%) of [4-(6-chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazine-1-yl]acetic acid tert-butyl ester.

D. [4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazine-1-yl]-acetic acid.

[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazine-1-yl]acetic acid tert-butyl ester (500 mg, 1.13 mmol) is dissolved in 1 mL of trifluoroacetic acid and 3 mL of CH_2Cl_2. The solvents are azeotropically removed with toluene. [4-(6-chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazine-1-yl]acetic acid (438 mg) is isolated as a white solid.\

E. 2-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-yl]-N-[2-(3H-imidazol-4-yl)-ethyl]acetamide.

To a slurry of [4-(6-chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazine-1-yl]acetic acid (47 mg, 0.12 mmol) in 2 mL of tetrahydrofuran is added Et_3N (0.025 mL, 0.18 mmol). The mixture is cooled to 0°C, and 1M solution of isopropyl chloroformate in toluene (0.12 mL, 0.12mmol) is added. The mixture is stirred for fifteen minutes and histamine (13.3 mg, 0.12 mmol) is added. The mixture is stirred overnight at room temperature. Reverse phase HPLC ($AcCN/H_2O$/TFA) affords 2-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-yl]-N-[2-(3H-imidazol-4-yl)-ethyl]acetamide trifluoroacetic acid salt (17 mg, 25%) as a solid. mp 77-82°C; MS m/z 482 (M+H).

The followin compounds are prepared from the appropriate starting materials using the method of EXAMPLE 823.

Example	Name	m/z [M+H]
824	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-pyridin-4-yl-acetamide	465, 467
825	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-pyridin-3-ylmethyl-acetamide	479, 481
826	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-piperidin-4-yl-acetamide	471, 473
827	N-(1-Carbamimidoyl-piperidin-4-yl)-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetamide	513, 515
828	5-(2-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetylamino}-ethyl)-imidazole-1-carboxylic acid ethyl ester	554, 556
829	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-pyrimidin-4-yl-acetamide	466, 468
830	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-phenyl-acetamide	464, 466
831	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(9H-purin-6-yl)-acetamide	506, 508
832	N-(4-Amino-2-methyl-pyrimidin-5-ylmethyl)-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetamide	509, 511
833	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(3-imidazol-1-yl-propyl)-acetamide	496, 498
834	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(1-methyl-1H-imidazol-4-yl)-ethyl]-acetamide	496, 498
835	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(2-pyridin-4-yl-ethyl)-acetamide	493, 495
836	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(3-methyl-3H-imidazol-4-yl)-ethyl]-acetamide	496, 498
837	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(2-pyridin-2-yl-ethyl)-acetamide	493, 495
838	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(2-pyridin-3-yl-ethyl)-acetamide	493, 495
839	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(2-imidazol-1-yl-ethyl)-acetamide	482, 484
840	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-	495, 497

	N-[2-(1-methyl-1H-pyrrol-2-yl)-ethyl]-acetamide	
841	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(5-methyl-1H-imidazol-4-yl)-ethyl]-acetamide	496, 498
842	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(4-dimethylamino-[1,3,5]triazin-2-yl)-acetamide	510, 512
843	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-methyl-N-pyridin-4-yl-acetamide	479, 481
844	N-[2-(2-Amino-pyridin-4-yl)-ethyl]-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetamide	508, 510
845	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(4-methyl-thiazol-5-yl)-ethyl]-acetamide	513, 515
846	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(2-thiazol-4-yl-ethyl)-acetamide	499, 501
847	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-(3-guanidino-propyl)-acetamide trifluoroacetic acid salt	487, 489
848	N-(3-Amino-propyl)-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetamide	445, 447
849	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(2-mercapto-1H-imidazol-4-yl)-ethyl]-acetamide	514, 516
850	N-[2-(2-Amino-thiazol-4-yl)-ethyl]-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-acetamide	514, 516
851	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-methyl-N-(2-pyridin-4-yl-ethyl)-acetamide	507, 509
852	2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-N-[2-(2-methylsulfanyl-1H-imidazol-4-yl)-ethyl]-acetamide	528, 530

EXAMPLE 853. 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[3-(3H-imidazol-4-yl)-propyl]-piperazin-2-one.

A. 3-Oxo-4-[3-(3-trityl-3H-imidazol-4-yl)-allyl-piperazine-1-carboxylic acid benzyl ester.

3-Oxo-piperazin-1-carboxylic acid benzyl ester (702 mg, 3.0 mmol) is dissolved in dimethylformamide (10 mL) and cooled to 0°C . Sodium hydride (60%, 148 mg, 3.7 mmol) is added, followed by the addition of 5-(3-chloro-propenyl)-1-trityl-1H-imidazole (473 mg, 1.2 mmol). The resulting mixture is left to stir at room temperature overnight. Most of the dimethylformamide is removed on the high vacuum. The reaction mixture is diluted with ethyl

acetate (250 mL) and quenched with water. The two layers are separated and ethyl acetate (2x 100 mL) is used to extract and dried over magnesium sulfate. The residue after filtration and concentration is chromatographed on silica gel (50% EtOAc/hexane) to give 3-oxo-4-[3-(3-trityl-3H-imidazol-4-yl)-allyl-piperazine-1-carboxylic acid benzyl ester (360 mg) as the desired product.

B. 4-[3-(3-tert-Butoxycarbonyl-3H-imidazol-4-yl)-allyl]-3-oxo-piperazine-1-carboxylic acid benzyl ester.

3-Oxo-4-[3-(3-trityl-3H-imidazol-4-yl)-allyl-piperazine-1-carboxylic acid benzyl ester (360 mg, 0.62 mmol) is stirred vigorously in a 30% solution of trifluoroacetic acid and methylene chloride (10 mL). After stirring for three hours, the trityl group is removed. The volatile solvents are removed in vacuo, and the crude product is taken-up in methylene chloride (10 mL). Pyridine (0.5 ml) and Di-tert-butyl dicarbonate (176 mg, 0.81 mmol) is added to the solution, and the resulting mixture is left to stir overnight. The reaction mixture is condensed and purified by flash column (SiO_2, 20% EtOAc/Hexane) to give 4-[3-(3-tert-butoxycarbonyl-3H-imidazol-4-yl)-allyl]-3-oxo-piperazine-1-carboxylic acid benzyl ester (100 mg).

C. 5-{3-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-propyl}-imidazol-1-carboxylic acid tert-butyl ester.

Palladium on carbon (10 %, 15 mg) is added to a solution of 4-[3-(3-tert-butoxycarbonyl-3H-imidazol-4-yl)-allyl]-3-oxo-piperazine-1-carboxylic acid benzyl ester (50 mg, 0.114 mmol) in 5 mL of methanol. The reaction mixture is left to stir in an atmosphere of hydrogen overnight. The palladium is filtered off, and the volatile solvents are removed on the rotovap. The crude product (50 mg, 0.114 mmol) is redissolved in methylene chloride (5 mL). Triethylamine (0.06 ml, 0.43 mmol) 6-chloro-benzo[b]thiophene-2-sulfonyl chloride (39 mg, 0.15 mmol) is added, and the resulting mixture is stirred overnight. The crude product is directly purified by flash column (SiO_2, 30% EtOAc/Hexane) to afford 5-{3-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-propyl}-imidazol-1-carboxylic acid tert-butyl ester (30 mg).

D. 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[3-(3H-imidazol-4-yl)-propyl]-piperazin-2-one:

5-{3-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-yl]-propyl}-imidazol-1-carboxylic acid tert-butyl ester (30 mg, 0.055 mmol) is stirred vigorously in a 30 % solution of trifluoroacetic acid and methylene chloride (2 mL). The reaction is complete after stirring for three hours. The volatile solvents are removed on the rotovap, and the gummy solid is titurated

with ether several times to afford 4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-1-[3-(3H-imidazol-4-yl)-propyl]-piperazin-2-one trifluoroacetic acid salt (30 mg) as a yellow solid. $C_{18}H_{19}ClN_4O_3S_2$ (m/z)+: 439, 441. Anal cald. for $C_{18}H_{19}ClN_4O_3S_2 \cdot C_2HF_3O_2$: C, 43.44; H, 3.65; N, 10.13. Found C, 42.03; H, 3.55; N, 8.26.

The following compounds are prepared using the methods described above.

Example	Name	m/z [M+H]
854	4-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-piperidine-1-carboxamidine	470, 472 Cl pattern
855	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(3-piperazin-1-yl-propyl)-piperazin-2-one	457, 459 Cl pattern
856	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(3-pyridin-4-yl-propyl)-piperazin-2-one	450, 452 Cl pattern
857	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-piperidin-4-yl-butyl)-piperazin-2-one	470, 472 Cl pattern
858	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(2-piperidin-4-yl-ethyl)-piperazin-2-one	442
859	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(3-piperidin-4-yl-propyl)-piperazin-2-one	456

EXAMPLE 860. 4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-piperazin-2-one.

A. 3-Methoxymethyl-4-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared by the method in EXAMPLE 66, Part A, substituting 5-(4-bromomethyl-phenyl)-2-methoxy-pyridine for 4-bromomethyl tolynitrile and 2-methoxymethyl-3-oxopiperazin-1-carboxylic acid benzyl ester for 3-oxopiperazin-1-carboxylic acid benzyl ester. MS (ISP) m/z 476, (M+H).

4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-piperazin-2-one

The title compound is prepared by deprotecting 3-methoxymethyl-4-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-oxo-piperazine-1-carboxylic acid benzyl ester as described in EXAMPLE 75, Part C. The crude amine is then coupled as described in EXAMPLE 123 with 3-(5-chloro-thiophen-2-yl)-(E)-acrylic acid, EXAMPLE 25. MS (ISP) m/z 516, 518, (M+H), Cl pattern.

The following compounds are prepared according to the method of Example 860.

Example	Name	m/z [M+H]
861	4'-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-biphenyl-2-carbonitrile	522, 524 Cl pattern
862	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-chloro-3-hydroxy-benzyl)-piperazin-2-one	471, 473 Cl pattern
863	1-Benzyl-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	421,423 Cl pattern
864	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-chloro-benzyl)-piperazin-2-one	455, 457 Cl pattern
865	4-[(4-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-piperazin-2-one	516, 518 Cl pattern
866	4-[(5-Chloro-thiophen-3-yloxy)-acetyl]-1-[4-(6-hydroxy-pyridin-3-yl)-benzyl]-3-(S)-methoxymethyl-piperazin-2-one	502, 504 Cl pattern
867	4-[(5-Chloro-thiophen-3-yloxy)-acetyl]-3-(S)-methoxymethyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-piperazin-2-one	516, 518 Cl pattern
868	4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-[4-(6-hydroxy-pyridin-3-yl)-benzyl]-3-(S)-methoxymethyl-piperazin-2-one	502, 504 Cl pattern
869	4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-(S)-methyl-piperazin-2-one	482
870	4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-3-(S)-methyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one	468
871	1-Biphenyl-4-ylmethyl-4-[3-(5-chloro-thiophen-2-yl)-(E)-acryloyl]-3(S)-ethyl-6-methyl-piperazin-2-one	
872	4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-1-[4-(6-hydroxy-pyridin-3-yl)-benzyl]-3-(S)-methoxymethyl-piperazin-2-one	498, 500 Cl pattern
873	4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-3-(S)-methoxymethyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-piperazin-2-one	512, 514 Cl pattern

EXAMPLE 874. 1-(3-Amino-1H-indazol-6-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one.

A. 2-Amino-4-(2-oxo-piperazin-1-ylmethyl)-benzonitrile.

To a solution of 4-(3-Amino-4-cyano-benzyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester hydrochloride (4.0 g, 10.0mmol) in CH_3OH (45 ml) and CH_2Cl_2 (10 ml) is added 10% Pd

on carbon (0.6 g). The mixture is stirred under an atmosphere of H_2 for 2 hours then is filtered through a pad of celite. The filtrate is concentrated and the residue purified by column chromatography eluting with 10% 7M NH_3 in CH_3OH / CH_2Cl_2 to yield the title compound (1.62 g, 7.0 mmol). ^1H NMR (DMSO,300MHz) δ 7.34 (d, 1H), 6.64 (s, 1H), 6.46 (d, 1H), 6.04 (bs, 2H), 4.40 (s, 2H), 3.28 (s, 2H), 3.14 (m, 2H), 2.87 (m, 2H), 2.77 (bs, 1H). MS (ion spray): m/z 231 $(M+H)^+$.

B. 2-Amino-4-[4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-benzonitrile.

To a cooled solution (0° C) of 2-Amino-4-(2-oxo-piperazin-1-ylmethyl)-benzonitrile (0.345 g, 1.5 mmol) in DMF (2 ml) is added finely powdered anhydrous K_2CO_3 (0.311 g, 2.25 mmol) and allowed to stir for 20 minutes. To this mixture is added a solution of 2-bromomethyl-benzo[b]thiophene (0.392 g, 1.5 mmol) in DMF (3 ml), the cold bath removed and allowed to stir for 2 hours. The reaction mixture is concentrated under high vacuum and the residue purified by column chromatography eluting with 55% EtOAc/ 5% CH_3OH/ hexane to yield the title compound (0.477 g, 1.16 mmol) as a white solid. ^1H NMR (DMSO,300MHz) δ 8.06 (d, 1H), 7.78 (d, 1H), 7.37 (m, 3H), 6.64 (s, 1H), 6.44 (d, 1H), 6.09 (bs, 2H), 4.42 (s, 2H), 3.88 (s, 2H), 3.21 (m, 4H), 2.72 (m, 2H). MS (ion spray): m/z 411, 413 $(M+H)^+$, Cl pattern.

C. 1-(3-Amino-1H-indazol-6-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one.

To a cooled solution (0° C) of 2-Amino-4-[4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-benzonitrile (0.365 g, 0.89 mmol) in concentrated HCl (2.1 ml) is added dropwise a solution of sodium nitrite (0.068 g, 0.98 mmol) in H_2O (0.2 ml). The reaction mixture is added to a cooled solution (0° C) of tin (II) chloride dihydrate (1.61 g, 7.12 mmol) in concentrated HCl (0.62 ml) and H_2O (3 ml). The precipitate is collected by vacuum filtration and dried under high vacuum. The crude solid is purified by column chromatography eluting with 10% 7M NH_3 in CH_3OH / CH_2Cl_2 to yield the title compound (0.144 g, 0.34 mmol) as a yellow solid. ^1H NMR (DMSO,300MHz) δ 11.35 (bs, 1H), 8.05 (d, 1H), 7.78 (d, 1H), 7.64 (d, 1H), 7.37 (m, 2H), 7.08 (s, 1H), 6.78 (d, 1H), 5.75 (s, 1H), 5.40 (bs, 1H), 4.58 (s, 2H), 3.88 (s, 2H), 3.20 (m, 4H), 2.70 (bt, 2H). MS (ion spray): m/z 426 $(M+H)^+$. Anal. cald. for $C_{21}H_{20}N_5OSCl;(H_2O)_{0.25}$: C, 58.6; H, 4.8; N, 16.3. Found C, 58.6; H, 4.7; N, 15.9. M.P.= 246-248°C.

EXAMPLE 875. 1-(3-Amino-1H-indazol-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)]-piperazin-2-one.

A. 2-Amino-4-[4-[3-(5-chloro-thiophen-2-yl)-allyl]-2-oxo-piperazin-1-ylmethyl)-benzonitrile.

Using essentially the same procedure as in EXAMPLE 874, Part B using 2-(3-bromo-propenyl)-5-chloro-thiophene is obtained the title compound. MS (EI): m/z 386, 388 (M^+), Cl pattern.

B. 1-(3-Amino-1H-indazol-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)]-piperazin-2-one.

Using essentially the same procedure as in EXAMPLE 874, Part C there is obtained the title compound. ^{1}H NMR (DMSO, 300MHz) δ 11.32 (bs, 1H), 7.62 (d, 1H), 7.06 (s, 1H), 7.02 (d, 1H), 6.96 (d, 1H), 6.78 (d, 1H), 6.67 (d, 1H), 5.96 (m, 1H), 5.32 (bs, 2H), 4.57 (s, 2H), 3.19 (bt, 2H), 3.12 (m, 4H), 2.64 (bt, 2H). MS (EI): m/z 401, 403 (M^+), Cl pattern. Anal. cald. for $C_{19}H_{20}ClN_5OS$: C, 56.8; H, 5.0; N, 17.4. Found C, 56.6; H, 4.8; N, 17.2. M.P.= 167-169°C

EXAMPLE 876. 1-(3-Amino-1H-indazol-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one.

A. 2-Amino-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperzin-1-ylmethyl]-benzonitrile.

Using essentially the same procedure as in EXAMPLE 874, Part B except using 6-chloro-benzo[b]thiophene-2-sulfonyl chloride, EXAMPLE 1, is obtained the title compound. MS (ion spray): m/z 461, 463 $(M+H)^+$, Cl pattern.

B. 1-(3-Amino-1H-indazol-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one.

Using essentially the same procedure as in EXAMPLE 874, Part C there is obtained the title compound. ^{1}H NMR (DMSO, 300MHz) δ 11.29 (s, 1H), 8.35 (s, 1H), 8.18 (s, 1H), 8.08 (d, 1H), 7.58 (m, 2H), 7.05 (s, 1H), 6.70 (d, 1H), 5.30 (bs, 2H), 4.56 (s, 2H), 3.84 (s, 2H), 3.40 (m, 2H), 3.30 (m, 2H). MS (ion spray): m/z 476, 478 $(M+H)^+$, Cl pattern. Anal. cald. for $C_{20}H_{18}ClN_5O_3S_2$: C, 50.5; H, 3.8; N, 14.7. Found C, 50.3; H, 3.6; N, 14.5. M.P.=274-276°C.

The following compounds are prepared using the procedures described above.

Example	Name	m/z
877	4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-2-(S)-methyl-3,6-dioxo-piperazin-1-ylmethyl]-benzamidine	441, 443 Cl pattern
878	4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-2-(R)-methyl-3,6-dioxo-	441, 443

	piperazin-1-ylmethyl]-benzamidine	Cl pattern
879	3-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-2,5-dioxo-piperazin-1-ylmethyl]-benzamidine	427, 429 Cl pattern
880	4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-2,5-dioxo-piperazin-1-ylmethyl]-benzamidine	427, 429 Cl pattern

Example 881: 5-Chloro-2-chlorosulfonyl-indole-1-carboxylic acid tert-butyl ester.

A. 5-Chloro-indole-1-carboxylic acid tert-butyl ester:

To a suspension of NaH (60%, 1.0 g, 25.2 mmol) in anhydrous THF (50 mL) at 0 °C is added 5-chloro-indole (2.73 g, 18.0 mmol). After 20 min, di-*t*-butyl dicarbonate (4.71 g, 21.6 mmol) is added and the reaction mixture is maintained at 0 °C for 4 h. The reaction mixture is partitioned between diethyl ether (100 mL) and saturated aqueous NH_4Cl (100 mL) and the layers are separated. The aqueous phase is extracted twice with diethyl ether (2 x 50 mL) and then the combined organic extracts are washed once with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product is purified by flash silica gel chromatography (hexane/EtOAc, 30:1 to 20:1) to provide 4.0 g (89%) of 5-chloro-indole-1-carboxylic acid tert-butyl ester as a colorless solid. ^1H NMR (300 MHz, $CDCl_3$) δ 1.66 (s, 9H), 6.50 (d, J = 3.5 Hz, 1H), 7.27 (m, 1H), 7.52 (s, 1H), 7.60 (d, J = 3.3 Hz, 1H), 8.06 (d, J = 8.6 Hz, 1H) ppm.

B. 5-Chloro-2-chlorosulfonyl-indole-1-carboxylic acid tert-butyl ester.

To a solution containing 5-chloro-indole-1-carboxylic acid tert-butyl ester (4.0 g, 15.9 mmol) in anhydrous THF (60 mL) at -78 °C is added 1.7 M *t*-BuLi in pentane (11.2 mL, 19.0 mmol) dropwise from a syringe. After 1 h at -78 °C, SO_2 gas is introduced into the reaction mixture for 5-10 min. The reaction mixture is warmed to ambient temperature and then concentrated to dryness *in vacuo*. The resulting solid is then suspended in hexane (80 mL), cooled to -60 °C, and SO_2Cl_2 (2.6 g, 19.0 mmol) is added dropwise.

After 16 h, the reaction mixture is concentrated to dryness and the residue is partitioned between EtOAc (100 mL) and aqueous $NaHCO_3$ (100 mL). The layers are separated and the organic phase is washed once with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product is purified by flash silica gel chromatography (hexane/EtOAc, 100:1 to 30:1) to afford 3.35 g (60%) of 5-chloro-2-chlorosulfonyl-indole-1-carboxylic acid tert-butyl ester as a off-white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 1.73 (s, 9H), 7.52 (dd, J = 9.1, 2.0 Hz, 1H), 7.60 (s, 1H), 7.69 (d, J = 2.0 Hz, 1H), 8.19 (d, J = 9.1 Hz, 1H) ppm.

Example 882: 6-Chloro-2-chlorosulfonyl-indole-1-carboxylic acid tert-butyl ester

A. 6-Chloro-indole-1-carboxylic acid tert-butyl ester.

To a suspension of NaH (60%, 0.41 g, 10.3 mmol) in anhydrous THF (20 mL) at 0 °C is added 6-chloro-indole (1.2 g, 7.4 mmol). After 10 min, di-*t*-butyl dicarbonate (1.93 g, 8.88 mmol) is added and the reaction mixture is slowly warmed to ambient temperature overnight. The reaction mixture is concentrated to dryness and the residue is partitioned between diethyl ether (100 mL) and saturated aqueous NH_4Cl (100 mL) and the layers are separated. The aqueous phase is extracted twice with diethyl ether (2 x 50 mL) and then the combined orgaic extracts are washed once with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product is purified by flash silica gel chromatography (hexane/EtOAc, 10:1) to provide 6.0 g (82%) of 6-chloro-indole-1-carboxylic acid tert-butyl ester as a colorless solid. ^1H NMR (300 MHz, $CDCl_3$) δ 1.66 (s, 9H), 6.52 (d, J = 3.6 Hz, 1H), 7.19 (dd, J = 8.3, 1.8 Hz, 1H), 7.45 (d, J = 8.3 Hz, 1H), 7.56 (d, J = 3.6 Hz, 1H), 8.18 (s, 1H) ppm.

B. 6-Chloro-2-chlorosulfonyl-indole-1-carboxylic acid tert-butyl ester.

To a solution containing 6-chloro-indole-1-carboxylic acid tert-butyl ester (2.1 g, 8.34 mmol) in anhydrous THF (30 mL) at -78 °C is added 1.7 M *t*-BuLi in pentane (6 mL, 10.2 mmol) dropwise from a syringe. After 1 h at -78 °C, SO_2 gas is introduced into the reaction mixture for 5-10 min. The reaction mixture is warmed to ambient temperature and then concentrated to dryness *in vacuo*. The resulting solid is then suspended in hexane (80 mL), cooled to -60 °C, and SO_2Cl_2 (0.81 g, 10.0 mmol) is added dropwise. After 16 h, the reaction mixture is concentrated to dryness and the residue is partitioned between diethyl ether (100 mL) and aqueous $NaHCO_3$ (100 mL). The layers are separated and the organic phase is washed once with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product is purified by flash silica gel chromatography (hexane/EtOAc, 100:1 to 30:1) to afford 5.34 g (64%) of 6-chloro-2-chlorosulfonyl-indole-1-carboxylic acid tert-butyl ester as a off-white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 1.74 (s, 9H), 7.35 (dd, J = 8.5, 1.8 Hz, 1H), 7.63 (m, 2H), 8.31 (m, 1H) ppm.

EXAMPLE 883. 3-(5-Chloro-thiophen-2-yl)-3-oxo-propionic acid tert-butyl ester.

A 0.25M THF solution of tert-butyl acetate (2.90 g, 25 mmol) is added dropwise to a cold (-78°C) solution of potassium bis(trimethylsilyl)amide (100 ml of a 0.5M toluene solution) and ethyl 5-chlorothiophene-2-carboxylate (Lancaster)(4.77 g, 25 mmol) in 50 ml of THF. The reaction is allowed to warm to 0°C over one hour. After stirring an additional hour at 0°C, the reaction is poured into 100 ml of a 1M HCl solution. The organic layer is extracted with brine

and evaporated *in vacuo*. The crude residue is purified by flash column chromatography eluting with 5% ethyl acetate/hexane to provide the product (4.54 g, 17 mmol) as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7,53 (d, 1H), 6.98 (d, 1H), 3.78 (3, 2H), 1.50 (s, 9H).

EXAMPLE 884 Methyl06-Chloro-benzofurancarboxylate.

A. 4-Chloro-2-hydroxy-benzylalcohol.

To 7 g of $LiAlH_4$ in 200 ml of THF is added portionwise 15 g of 4-chlorosalicylic acid. The resulting mixture is heated under reflux for one hour, cooled and stirred at room temperature for 21 hours. Water (7 ml) in THF (50 ml) is added dropwise, followed by 1N hydrochloric acid (250 ml), concentrated hydrochloric acid (50 ml) and ethyl acetate (200 ml). After filtration on a pad of celite the two layers are separated, the organic layer washed with brine, dried over magnesium sulfate, concentrated. The brown oil is dissolved in iso-propyl ether and filtered on a short column of silica gel. After concentration the solid is crystallized in cyclohexane, filtered, washed and dried to give 4-chloro-2-hydroxy-benzylalcohol as a white solid (9.7 g, 70% yield)

$C_7H_7ClO_2$ MS ($M^{+\cdot}$) m/z: 158, 160, Cl pattern.

B. Ethyl-(2-hydroxymethyl-5-chloro-phenoxy)-acetate.

To a solution of 4-chloro-2-hydroxy-benzylalcohol (9.7 g, 61.3 mmol) in 100 ml of DMF is added potassium carbonate (17 g, 123.1 mmol), and the resulting suspension is stirred for 15 minutes at room temperature. Ethyle bromoacetate (7.96 ml, 67 mmol) is added and the mixture is stirred at room temperature for two days. The mixture is poured in 500 ml of water, extracted with ethyl acetate (500 ml). The ethyl acetate layer is separated, washed with water (500 ml), brine (500ml) and dried over magnesium sulfate. After concentration ethyl-(2-hydroxymethyl-5-chloro-phenoxy)-acetate is obtained as a white solid (13.7 g, 91 % yield)

$C_{11}H_{13}ClO_4$, MS ($M^{+\cdot}$) m/z: 244, 246, Cl pattern.

C. Ethyl-(2-formyl-5-chloro-phenoxy)-acetate.

Ethyl-(2-hydroxymethyl-5-chloro-phenoxy)-acetate (2.44 g, 10 mmol) is dissolved in 40 ml of chloroform. Activated manganese (IV) oxyde (8.7 g ,100 mmol) is added in two portions and the resulting suspension is stirred at room temperature for 5 hours. After fitration on a pad of celite and concentration ethyl-(2-formyl-5-chloro-phenoxy)-acetate (2.18 g , 90% yield) is obtained as a pale yellow oil.

$C_{11}H_{11}ClO_4$, MS $(M+H)^+$: 243, Cl pattern.

D. Methyl-6-chloro-benzofurancarboxylate

Magnesium (1.2 g, 50 mmol) is dissolved in 40 ml of methanol. A solution of ethyl-(2-formyl-5-chloro-phenoxy)-acetate (2.1 g , 8.65 mmol) in 15 ml of methanol is added and the resulting mixture is heated under reflux for one hour, cooled , poured in 1N hydrochloric acid (150ml). After stirring at room temperature the yellow solid is filtered, washed thoroughly with water and dried. Methyl-6-chloro-benzofurancarboxylate is obtained as a yellow solid (0.835 g , 46 % yield).

$C_{10}H_7ClO_3$, MS (M^+) : 210, Cl pattern

EXAMPLE 885. 2-Cyclopentyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as in EXAMPLE 41, sustitituting CBZ-1-amino-cyclopentyl-1-caboxylic acid for Cbz-O-methyl-serine. ^1H NMR (CD_3OD, 300MHz) δ 7.32 (m, 5H), 5.12 (s, 2H), 3.71 (m, 2H), 3.28 (m, 2H), 2.17 (m, 4H), 1.8 (m, 4H). MS (ion spray) m/z 289, (M+H).

EXAMPLE 886 (+/-)-cis-4-benzyloxycarbonyl-decahydroquinoxalin-2-one.

A. (+/-)-cis-decahydroquinoxalin-2-one.

cis-1,2-Diaminocyclohexane (4.1 g, 36 mmol) is dissolved in 150 ml of H_2O. Chloroacetic acid (3.4 g, 36 mmol) in 50 ml of H_2O is added dropwise at 10° C in 5 minutes, then potassium carbonate (7.9 g , 57 mmol) in 30 ml of H_2O is added dropwise at 10 C. The reaction mixture is allowed to warm slowly to room temperature and stirred 24 hours. The solution is heated at 90°C for 2 hours, concentrated. The resulting solid is taken-up in boiling toluene (100 ml), filtered while hot, concentrated to give (+/-)-cis-decahydroquinoxalin-2-one (0.8 g, 14% yield) as a white solid.

$C_8H_{14}N_2O$, MS (M+H)+ : 155

B. (+/-)-cis-4-benzyloxycarbonyl-decahydroquinoxalin-2-one.

(+/-)-cis-decahydroquinoxalin-2-one (0.8 g, 5.19 mmol) is suspended in 25 ml of H_2O. $NaHCO_3$ (0.87 g, 10.35 mmol) is added and the reaction mixture is cooled to 10° C. Benzylchloroformate (1 ml, 6.68 mmol) is added dropwise to the vigorously stirred mixture. After 20 hours at room temperature the solid is filtered, washed thoroughly with H_2O, air-dried. The title compound (1.46g, 98 % yield) is obtained as a white solid.

$C_{16}H_{20}N_2O_3$, MS $(M+H)^+$: 289

EXAMPLE 887 5-Methyl-3-oxo-2-propyl-piperazine-1-carboxylic acid tert-butyl ester.

A. [1-(Methoxy-methoxyl-methyl-carbamoyl]-carbamic acid benzyl ester.

To a solution of N-Cbz-L-alanine (12.9 g, 66.7 mmol) and N,O-dimethyl hydroxyl amine hydrochloride (7.2 g, 73.8 mmol) in CH_2Cl_2 (200mL) is added TBTU (21.43 g, 66.7 mmol) and diisopropyl ethyl amine (25.9 g, 231.5 mmol). After 6 h, the solution is diluted with CH_2Cl_2 (200mL) and is washed with 1N HCl, H_2O, and sat. NaCl. The organic layer is dried over MgSO4, filtered and concentrated to give the title compound as an oil. MS (EI) m/z 266, (M+).

B. [1-Methyl-2-oxo-ethyl]-carbamic acid benzyl ester.

To a solution of [1-(methoxy-methoxyl-methyl-carbamoyl]-carbamic acid benzyl ester (66.7 mmol) in THF (160mL) is added a 1.0M solution of lithium aluminum hydride in THF (81.1 mmol, 81.1mL) dropwise at 0°C. After 20 min., 1N $KHSO_4$ is added drpwise. The solution is diluted with H_2O (200mL) and the pH is adjusted to 3 with 1N $KHSO_4$. The resulting solution is extracted with Et_2O. The Et2O extracts are wshed with H2O and sat. NaCl. The organic layer is dried over MgSO4, filtered and concentrated to give the title compound (12g, 66 mmol) of the title compound. MS (EI) m/z 177, (M+).

C. 2-[2-Benzyloxycarbonylamino-propylamino]-pentanoic acid methyl ester.

To a solution of [1-methyl-2-oxo-ethyl]-carbamic acid benzyl ester (12.3 g, 69 mmol) and norvaline methylester hydrochloride (11.6 g, 69mmol) in MeOH (300mL) is added diisopropyl ethyl amine (9.4 g, 73 mmol) and 2 drops of acetic acid. After 10 min., $ZnCl_2$ (9.46 g, 69mmol) and sodium cyanoborohydride (8.72g, 14 mmol) is added. The solution is stirred at ambient for 16 h. The solution is then concentrated. The residue is dissolved in EtOAc and 1N $KHSO_4$. The oraganic layer is washed with 1N $KHSO_4$, H_2O, and sat. NaCl. The organic layer is dried over $MgSO_4$, filtered and concentated. The crude product is purified by column chromatograghy eluting with a gradient of 20% EtOAc/hexane to 40% EtOAc/hexanes. The title compound (8.6 gm, 26.6 mmol) isobtained as a foam. MS (ion spray) m/z 323, (M+H).

D. 5-Methyl-3-oxo-2-propyl-piperazine-1-carboxylic acid tert-butyl ester.

A solution of 2-[2-benzyloxycarbonylamino-propylamino]-pentanoic acid methyl ester (6.6g, 20.5 mmol) in MeOH (100mL) is added 4 drops of AcOH and 0.65g of 10% Pd/C. The atmosphere above the reaction is replaced by hydrogen. The reaction is stirred overnight. The solution is then filtered to give a clear solution. The solution is concentrated and the residue is

dissolved in EtOH. The solution is heated to reflux for 2 h. After this time the ethanolic solution is concentrated. The residue is dissolved in CH_2Cl_2 (60 mL) and BOC_2O (3.3 g, 15.1 mmol) followed by DMAP (0.16 g, 1.3 mmol) are added. After 16 h, the reaction is diluted with CH_2Cl_2 (150mL)and washed with 1N KHSO4, H2O and sat. NaCl. The organic layer is dried over $MgSO_4$, filtered and concentrated to give the title compound (3.1 g, 12.1 mmol) as a white solid. ^1H NMR ($CDCl_3$, 300MHz) δ 7.78 (s, 1H), 4.36 (m, 1H), 4.02 (m, 1H), 3.48 (m, 2H), 2.49 (m, 1H), 1.77 (m, 1H), 1.55 (m, 1H), 1.39 (s, 9H), 1.02 (d, 3H), 0.8 (m, 3H). MS (ion spray) m/z 257, (M+H).

EXAMPLE 888 4-[4-Amino-quinazolin-7-ylmethyl]-5-methyl-3-oxo-2-propyl-piperazine

A. 3-[3-Amino-4-cyanobenzyl]-2-propyl-5-methyl-3-oxo-piperazine-1-carboxylic acid tert-butyl ester.

To a solution of 5-methyl-3-oxo-2-propyl-piperazine-1-carboxylic acid tert-butyl ester (3.07 g, 12 mmol), prepared as described in EXAMPLE 887, in THF (150 mL) is added t-BuOK (1.3 g, 11 mmol). The solution is stirred at ambient temperatures for 25 min. After this time, the reaction mixture is cooled to 0°C and 2-amino-4-bromomethyl-benzonitrile (2.9 g, 11.3 mmol) and 18-C-6 (15 mgs) are added. The solution is allowed to warm to ambient temperatures and is stirred for 16 h. After this time, 0.5 mL of a saturated NH_4Cl solution is added. The solution is concentrated. The residue is purified by column chromatograghy eluting with 20% EtOAc/CH_2Cl_2 to give the title compound as a white solid.
MS (ion spray) m/z 387, (M+H).

B. 4-[4-Amino-quinazolin-7-ylmethyl]-5-methyl-3-oxo-2-propyl-piperazine-1-carboxylic acid tert-butyl-ester.

To a solution of 3-[3-amino-4-cyanobenzyl]-2-propyl-5-methyl-3-oxo-piperazine-1-carboxylic acid tert-butyl ester (1.16 g, 3.0 mmol) in ethanol (30 mL) is added acetic acid (0.55 g, 9.0 mmol) and triazine (0.73 g, 9.0 mmol). The solution is refluxed overnight. After this time, the solution is concentrated. The residue is purified by column chromatography eluting with 5% MeOH/ CH_2Cl_2 to give the title compound (0.91 g) as a white solid.
MS (ion spray) m/z 414, (M+H).

C. 4-[4-Amino-quinazolin-7-ylmethyl]-5-methyl-3-oxo-2-propyl-piperazine.

To a solution of 4-[4-amino-quinazolin-7-ylmethyl]-5-methyl-3-oxo-2-propyl-piperazine-1-carboxylic acid tert-butyl-ester (0.91 g, 2.2 mmol) in EtOAc (40 mL) is bubbbled HCl (gas) for

5 min. at 0°C. After this time, the solution is stirred at ambient temperatures for 15 min. The solution is concentrated. The residue is purified by column chromatograpghy eluting with 1:5:100 NH_4OH/MeOH/CH_2Cl_2. The title compound (0.5 g) is obtained as a white solid. ^1H NMR (300 MHz, CDOD) δ 8.40 (s, 1H), 8.04 (d, 1H), 7.52 (s, 1H), 7.36 (m, 1H), 5.10 (d, 1H), 4.45 (d, 1H), 3.55 (m, 2H), 3.10 (m, 1H), 2.81 (m, 1H), 1.90 (m, 1H), 1.72 (m, 1H), 1.44 (m, 2H), 1.29 (d, 3H), 0.96 (m, 3H).

MS (ion spray) m/z 314, (M+H).

Example 889: (*R*)-3-Methoxymethyl-5-oxo-piperazine-1-carboxylic acid allyl ester

A. (*S*)-2-Benzyloxycarbonylamino-3-methoxy-propionic acid methyl ester.

A solution containing Z-L-serine (30 g, 0.126 mol) in anhydrous DMF (500 mL) is cooled to 0 °C. Sodium hydride (60%, 11.05 g, 0.28 mol) is added portionwise over ~20 min and the mixture is left to stir for 1 h. Methyl iodide (23.5 mL, 0.38 mol) is added and the mixture is stirred for 30 min at 0 °C and then at room temperature for 2.5 h after which time TLC indicated complete consumption of starting material. Water (1200 mL) is added and the mixture is extracted with diethyl ether (4 x 200 mL). The combined organic extracts are washed with brine (2 x 200 mL), dried over anhydrous Na_2SO_4 and concentrated to afford 30 g of crude (*S*)-2-benzyloxycarbonylamino-3-methoxy-propionic acid methyl ester as a pale yellow oil.

B. (*R*)-(1-Hydroxymethyl-2-methoxy-ethyl)-carbamic acid benzyl ester.

Calcium chloride (16.63 g, 149.8 mmol) is added to a stirring suspension of sodium borohydride (11.33 g, 299.6 mmol) in ethanol (300 mL) at -40 °C. The heterogeneous mixture is warmed to -20 °C and stirred for 1 h. (*S*)-2-Benzyloxycarbonylamino-3-methoxy-propionic acid methyl ester (20 g, 74.9 mmol) in abs EtOH (250 mL) is then added via cannula transfer. The heterogeneous mixture is stirred at -20 °C for 3 h. The reaction is quenched with water (400 mL) and carefully acidified with 1. 0 M HCl. The aqueous layer is extracted with CH_2Cl_2 (4 x 200 mL) and the combined organic phases are washed with brine (200 mL), dried over anhydrous Na_2SO_4 and concentrated to afford a colorless oil. The mixture is absorbed onto the silica gel and chromatographed on silica gel (hexane:EtOAc, 4:1 > 2:1 > 1:1 > 1:2) to afford 11.5 g (64%) of (*R*)-(1-hydroxymethyl-2-methoxy-ethyl)-carbamic acid benzyl ester as a colorless oil.

C. (*S*)-(1-Formyl-2-methoxy-ethyl)-carbamic acid benzyl ester.

To a solution of DMSO (3.56 mL, 50.21 mmol) in anhydrous CH_2Cl_2 (50 mL) at -78 °C is added 2.0 M oxalyl chloride in CH_2Cl_2 (12.55 mL, 25.1 mmol) via syringe. The mixture is stirred at -78 °C for 10 min, then a solution of (*R*)-(1-hydroxymethyl-2-methoxy-ethyl)-carbamic acid benzyl ester (5 g, 20.92 mmol) in anhydrous CH_2Cl_2 (100 mL) is added via cannula transfer. The mixture is stirred at -78 °C for 30 min. Triethylamine (14.6 mL, 104.6 mmol) is added and the mixture is placed in a 0 °C bath. The reaction is complete in 10 min.
The mixture is quenched with saturated $NaHSO_4$ (200 mL) and the product is extracted with CH_2Cl_2 (4 x 100 mL). The combined organic extracts are washed with brine (100 mL), dried over Na_2SO_4, and concentrated to afford (*S*)-(1-formyl-2-methoxy-ethyl)-carbamic acid benzyl ester as a yellow oil which is used without further purification. ^1H NMR (300 MHz, $CDCl_3$) δ 3.32 (s, 3H), 3.63 (dd, J = 9.6, 4.5 Hz, 1H), 3.93 (dd, J = 9.6, 3.3 Hz, 1H), 4.36 (m ,1H), 5.13 (s, 2H), 5.68 (br d, 1H), 7.29-7.37 (m, 5H), 9.60 (s, 1H) ppm.

D. (*R*)-(2-Benzyloxycarbonylamino-3-methoxy-propylamino)-acetic acid methyl ester.

To a solution of glycine methyl ester HCl (10.51 g, 83.68 mmol) in anhydrous MeOH (100 mL) at 0 °C is added a solution of (*S*)-(1-formyl-2-methoxy-ethyl)-carbamic acid benzyl ester (20.92 mmol) in anhydrous MeOH (20 mL). The solution is stirred at 0 °C for 10 minutes, then 1.0 M $NaBH_3CN$ in THF (31.38 mL, 31.38 mmol) is added and the now heterogeneous mixture is allowed to warm to room temperature and stir overnight. The mixture is concentrated to dryness, then partitioned between $NaHCO_3$ (200 mL) and EtOAc (200 mL). The layers are separated and the aqueous layer is extracted twice with EtOAc (100 mL) and the combined organic phases are washed with brine (100 mL), dried over Na_2SO_4, and concentrated to afford a yellow oil which is absorbed onto silica gel and chromatographed (CH_2Cl_2 => 1% MeOH/CH_2Cl_2 => 2% MeOH/CH_2Cl_2) to afford 3.9 g (60%) of *R*-(2-benzyloxycarbonylamino-3-methoxy-propylamino)-acetic acid methyl ester as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.73 (br s, 1H), 2.71 (dd, J = 12.1, 5.7 Hz, 1H), 2.84 (dd, J = 12.2, 5.7 Hz, 1H), 3.32 (s, 3H), 3.39 (d, J = 8.6 Hz, 2H), 3.40-3.52 (m, 2H), 3.70 (s, 3H), 3.82 (m, 1H), 5.09 (s, 2H), 5.35 (br d, 1H), 7.25-7.35 (m, 5H) ppm. Mass spectrum (ion spray): *m/z* 331 (M+H).

E. (*R*)-6-methoxymethyl-piperazin-2-one.

(*R*)-(2-Benzyloxycarbonylamino-3-methoxy-propylamino)-acetic acid methyl ester (3.9 g, 12.58 mmol) is dissolved in MeOH (~200 mL) and warmed in the presence of decolorizing charcoal for 1 h. The mixture is filtered through celite and the clear filtrate is concentrated. The residue is redissolved in MeOH (160 mL) and placed in a Parr bottle. Palladium-on-carbon (10%, 800 mg) is added and the mixture is hydrogenated for 5 h at 45 PSI. An additional

portion of Pd-on-C (250 mg) is added and the mixture left is reacted for 16 h at 45 PSI. The mixture is filtered through celite and concentrated to afford 1.5 g (83%) of (*R*)-6-methoxymethyl-piperazin-2-one as a yellow solid which is used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1,77 (br s, 1H), 2.70 (dd, J = 13.1, 7.2 Hz, 1H), 3.07 (dd, J = 13.1, 4.5 Hz, 1H), 3.26 (dd, J = 9.1, 7.7 Hz, 1H), 3.33 (s, 3H), 3.37-3.45 (m, 3H), 3.61 (m , 1H), 6.51 (br s, 1H) ppm.

F. (*R*)-3-Methoxymethyl-5-oxo-piperazine-1-carboxylic acid allyl ester.

(*R*)-6-methoxymethyl-piperazin-2-one (2.3 g, 16.0 mmol) is dissolved in anhydrous CH_2Cl_2 (60 mL) and cooled to 0 °C. Triethylamine (3.4 mL, 24.0 mmol) is added, followed, after 5 minutes, by allyl chloroformate (2.0 mL, 19.2 mmol). The mixture is allowed to warm to room temperature over 2 h when TLC analysis indicated that the reaction is complete.
The mixture is partitioned between water (100 mL) and CH_2Cl_2 (100 mL) and the layers are separated. The aqueous phase is extracted twice with CH_2Cl_2 (2 x 75 mL) and the combined organic phases are washed with brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated to afford the crude product which is purified by flash silica gel chromatography (CH_2Cl_2 to 1%, 2%, 4% MeOH/CH_2Cl_2) to afford 3.41 g (93%) of (*R*)-3-methoxymethyl-5-oxo-piperazine-1-carboxylic acid allyl ester as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.26 (dd, J = 9.3, 7.4 Hz, 1H), 3.31 (s, 3H), 3.36 (m, 1H), 3.63 (m, 1H), 3.76 (m, 1H), 4.07 (ABq, Δ_{AB} = 39.9 Hz, J_{AB} = 18.5 Hz, 2H), 4.58 (d, J = 5.59 Hz, 2H), 5.21 (m, 2H), 5.88 (m, 1H), 7.05 (br, 1H) ppm.

Example 890: 6-Isopropyl-piperazin-2-one.

A. (*R*)-2-Benzyloxycarbonylamino-3-methyl-thiobutyric acid S-ethyl ester.

To a solution containing (*R*)-2-benzyloxycarbonylamino-3-methyl-butyric acid (5.0 g, 20.0 mmol) in anhydrous CH_2Cl_2 (20 mL) is added DMAP (258 mg, 2.0 mmol) followed by chilled EtSH (1.6 mL, 22.0 mmol). Dicyclohexylcarbodiimide (4.5 g, 22.0 mmol) is added in one portion and the reaction is complete after 30 min. The solid material is removed by vacuum filtration and the filtrate is concentrated. The crude product is purified by flash silica gel chromatography (hexane to 8:1 hexane/EtOAc) to provide (*R*)-2-benzyloxycarbonylamino-3-methyl-thiobutyric acid S-ethyl ester (5.21 g, 88%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H), 1.23 (t, J = 7.5 Hz, 3H), 2.27 (m, 1H), 2.88 (q, J = 7.5 Hz, 2H), 4.35 (dd, J = 9.5, 4.6 Hz, 1H), 5.13 (s, 2H), 5.25 (br d, J = 9.5 Hz, 1H), 7.30-7.36 (m, 5H) ppm.

B. (*R*)-(1-Formyl-2-methyl-propyl)-carbamic acid benzyl ester.

To a solution containing (*R*)-2-benzyloxycarbonylamino-3-methyl-thiobutyric acid S-ethyl ester (5.2 g, 17.6 mmol) in acetone (100 mL) is added Pd-on-C (10%, 233 mg). The heterogeneous mixture is cooled to 0 °C and Et_3SiH (8.4 mL, 53 mmol) is quickly added. After 30 min, the reaction mixture is filtered through a pad of celite and the clear filtrate is concentrated to a residue which is partitioned between hexane (200 mL) and acetonitrile (300 mL). The layers are separated and the ACN phase is washed once with hexane (100 mL) and then concentrated to afford crude (*R*)-(1-Formyl-2-methyl-propyl)-carbamic acid benzyl ester (4.13 g) which is used directly without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30 (m, 1H), 4.31 (m, 1H), 5.09 (s, 2H), 5.45 (br, 1H), 7.30-7.45 (m, 5H), 9.65 (s, 1H) ppm.

C. (*R*)-(2-Benzyloxycarbonylamino-3-methyl-butylamino)-acetic acid ethyl ester.

To a solution containing crude (*R*)-(1-formyl-2-methyl-propyl)-carbamic acid benzyl ester (4.13 g, 17.6 mmol) in anhydrous MeOH (100 mL) at 0 °C is added glycine ethyl ester hydrochloride (9.5 g, 70.4 mmol). After 10 min, 1.0 M $NaCNBH_3$ in THF (27 mL, 27 mmol) is added and the heterogeneous reaction mixture is allowed to warm to ambient temperature overnight.

The reaction mixture is concentrated and the residue is partitioned between diethyl ether (200 mL) and saturated aqueous $NaHCO_3$ (200 mL). The layers are separated and the aqueous layer is extracted twice with diethyl ether (2 x 200 mL). The combined organic extracts are washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to afford the crude product which is purified by flash silica gel chromatography (hexane/EtOAc, 2:1 to 1:1) which provided 4.2 g (74%) of (*R*)-(2-benzyloxycarbonylamino-3-methyl-butylamino)-acetic acid ethyl ester as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, J = 7.0 Hz, 3H), 0.92 (d, J = 7.0 Hz, 3H), 1.25 (t, J = 8.4 Hz, 3H), 1.62 (br s, 1H), 1.80 (m, 1H), 2.65-2.70 (m, 2H), 3.37 (ABq, Δ_{AB} = 32.3 Hz, J_{AB} = 17.4 Hz, 2H), 4.16 (q, J = 8.4 Hz, 2H), 5.14 (s, 2H), 7.28-7.36 (m, 5H) ppm. Mass spectrum (ion spray): *m/z* 323 (M+H).

D. (*R*)-6-Isopropyl-piperazin-2-one.

To a Parr vessel charged with (*R*)-(2-benzyloxycarbonylamino-3-methyl-butylamino)-acetic acid ethyl ester (4.2 g, 13.0 mmol) in MeOH (130 mL) is added Pd-on-C (10%, 396 mmol). The reaction vessel is pressurized with 40 PSI hydrogen pressure and shaken for 4 h at ambient temperature. The reaction mixture is then filtered through celite and the filtrate is concentrated to provide 1.77 g (95%) of (*R*)-6-isopropyl-piperazin-2-one as an off-white solid which is used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (d, J = 6.8 Hz, 3H),

0.97 (d, J = 6.8 Hz, 3H), 1.68 (sept, J = 6.7 Hz, 1H), 2.67 (dd, J = 12.8, 8.9 Hz, 1H), 3.09-3.22 (m, 2H), 3.46 (ABq, Δ_{AB} = 34.3 Hz, J_{AB} = 17.5 Hz, 2H), 5.97 (br s, 1H) ppm.

EXAMPLE 891 9-(4-Aminoquinazolin-7-ylmethyl)-6,9-diaza-spiro[4,5]decan-10-one.

The title compound is prepared as described in EXAMPLE 75, substituting 2-cyclopentyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, Example 885, for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. ^{1}H NMR (CD_3OD, 300MHz) δ 8.38 (s, 1H), 8.09 (d, 1H), 7.56 (s, 1H), 7.39 (d, 1H), 4.72 (s, 2H), 3.38 (m, 2H), 3.07 (m, 2H), 2.21 (m, 2H), 1.72 (m, 6H).

EXAMPLE 892 (+/-)-cis-4-benzyloxycarbonyl-decahydroquinoxalin-2-one.

A. (+/-)-cis-decahydroquinoxalin-2-one.

cis-1,2-Diaminocyclohexane (4.1 g, 36 mmol) is dissolved in 150 ml of H_2O. Chloroacetic acid (3.4 g, 36 mmol) in 50 ml of H_2O is added dropwise at 10° C in 5 minutes, then potassium carbonate (7.9 g , 57 mmol) in 30 ml of H_2O is added dropwise at 10 C. The reaction mixture is allowed to warm slowly to room temperature and stirred 24 hours. The solution is heated at 90°C for 2 hours, concentrated. The resulting solid is taken-up in boiling toluene (100 ml), filtered while hot, concentrated to give (+/-)-cis-decahydroquinoxalin-2-one (0.8 g, 14% yield) as a white solid.

$C_8H_{14}N_2O$, MS (M+H)+ : 155

B. (+/-)-cis-4-benzyloxycarbonyl-decahydroquinoxalin-2-one.

(+/-)-cis-Decahydroquinoxalin-2-one (0.8 g, 5.19 mmol) is suspended in 25 ml of H_2O. $NaHCO_3$ (0.87 g, 10.35 mmol) is added and the reaction mixture is cooled to 10° C. Benzylchloroformate (1 ml, 6.68 mmol) is added dropwise to the vigorously stirred mixture. After 20 hours at room temperature the solid is filtered, washed thoroughly with H_2O, air-dried. The title compound (1.46g, 98 % yield) is obtained as a white solid.

$C_{16}H_{20}N_2O_3$, MS $(M+H)^+$: 289

EXAMPLE 893 (+/-)-cis-1-(4-Amino-quinazolin-7-ylmethyl)-decahydroquinoxalin-2-one.

The title compound is prepared as described in EXAMPLE 75, subsituting (+/-)-cis-4-benzyloxycarbonyl-decahydroquinoxalin-2-one EXAMPLE 892 for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. $C_{17}H_{21}N_5O$, MS $(M+H)^+$: 312

EXAMPLE 894 (+/-)-trans-4-benzyloxycarbonyl-decahydroquinoxalin-2-one

A. (+/-)-trans-decahydroquinoxalin-2-one.

(+/-)-trans-1,2-Diaminocyclohexane (22.84 g, 200 mmol) is dissolved in 600 ml of H_2O. Chloroacetic acid (18.8 g, 200 mmol) in 200 ml of H_2O is added dropwise at 10° C in 30 minutes, then potassium carbonate (44 g , 320 mmol) in 120 ml of H_2O is added dropwise at 10 C. The reaction mixture is allowed to warm slowly to room temperature and stirred 24 hours. The solution is heated at 90° C for 2 hours, concentrated. The resulting solid is taken-up in boiling EtOH (800 ml), filtered while hot, concentrated. The off-white solid is recrystallized in boiling toluene (1000 ml), dried to give(1) (9.72 g, 31% yield) as a white solid.

$C_8H_{14}N_2O$, MS (M+H)+ : 155

B. (+/-)-trans-4-benzyloxycarbonyl-decahydroquinoxalin-2-one.

(+/-)-trans-4-Benzyloxycarbonyl-decahydroquinoxalin-2-one (0.8 g, 5.19 mmol) is suspended in 25 ml of H_2O. $NaHCO_3$ (0.87 g, 10.35 mmol) is added and the reaction mixture is cooled to 10° C. Benzylchloroformate (1 ml, 6.68 mmol) is added dropwise to the vigorously stirred mixture. After 5 hours at room temperature the solid is filtered, washed thoroughly with H_2O, air-dried. The title compound (1.33 g, 89 % yield) is obtained as a white solid.

EXAMPLE 895 (+/-)-trans-1-(4-Amino-quinazolin-7-ylmethyl)-decahydroquinoxalin-2-one.

The title compound is prepared as described in EXAMPLE 75, subsituting trans-4-benzyloxycarbonyl-decahydroquinoxalin-2-one (EXAMPLE 894) for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

$C_{17}H_{21}N_5O$, MS $(M+H)^+$: 312

EXAMPLE 896 4-Benzyloxycarbonyl-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one.

A. [1-(2,2-Dimethoxy-ethylcarbamoyl)-3-(S)-methylsulfanyl-propyl]-carbamic acid benzyl ester

To a solution of (L)-N-Benzyloxycarbonyl-methionine (25g, 88.2 mmol) in 400 ml of CH_2Cl_2 is added TBTU (28.3 g, 88.2 mmol), followed by NEt_3 (36.6 ml, 264 mmol) and aminoacetaldehyde dimethylacetal (10.6 ml, 69.7 mmol). The solution is stirred for 16 hours, washed with H_2O, 1N hydrochloric acid, saturated aqueous $NaHCO_3$, brine, dried over magnesium sulfate and concentrated. The resulting crude product is purified by column chromatography eluting with a gradient of 1%MeOH:CH_2Cl_2 to 5%MeOH:CH_2Cl_2. The title compound (23.3 g, 71% yield) is obtained as a white solid.

$C_{17}H_{26}N_2O_5S$ MS $(M+H)^+$: 371

B. 4-Benzyloxycarbonyl-3-(S)-(2-methylsulfanyl-ethyl)-3,4-dihydro-1H-pyrazine-2-one

To a solution of [1-(2,2-dimethoxy-ethylcarbamoyl)-3-(S)-methylsulfanyl-propyl]-carbamic acid benzyl ester (23.3 g, 63 mmol) in toluene (300 ml) is added p-toluenesulfonic acid monohydrate (1.14 g , 6.3 mmol). The resulting solution is stirred at 70°C for 4 hours, cooled, washed with H_2O, brine, dried over magnesium sulfate and concentrated. The resulting crude product is purified by column chromatography eluting with a gradient of 2%MeOH:CH_2Cl_2 to 5%MeOH:CH_2Cl_2. The title compound (17.9 g, 93% yield) is obtained as an oil.

$C_{15}H_{18}N_2O_3S$ MS $(M+H)^+$: 307

C. 4-Benzyloxycarbonyl-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one.

To a solution of 4-benzyloxycarbonyl-3-(S)-(2-methylsulfanyl-ethyl)-3,4-dihydro-1H-pyrazine-2-one (0.3 g, 1 mmol) in CH_2Cl_2 is added Et_3SiH (1.57 ml, 10 mmol). The resulting solution is cooled to 0° C and CF_3CO_2H (2.2 ml, 30 mmol) is added dropwise. The mixture is stirred 16 hours at room temperature, washed with a saturated aqueous $NaHCO_3$ solution, brine. The solution is dried over $MgSO_4$, concentrated. The resulting crude product is purified by column chromatography on silica gel eluting with a gradient of 50% AcOEt:Hexane to 100 % AcOEt. The title compound (0.138 g, 46 % yield) is obtained as an oil.

$C_{15}H_{20}N_2O_3S$ MS $(M+H)^+$: 309

EXAMPLE 897 1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one.

A. 4-Benzyloxycarbonyl-1- [3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one.

To a solution of 4-benzyloxycarbonyl-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one (1.15 g, 3.74 mmol) in 10 ml of DMF is added at 0°C sodium hydride (164 mg at 60% in oil, 4.12 mmol). The solution is stirred 10 minutes then 2-(benzhydrylidene-amino)-4-bromomethyl-benzonitrile (2.6 g at 52%, 3.74 mmol) in 25 ml of DMF is added dropwise. The resulting mixture is stirred for 20 hours at room temperature, diluted with ethyle acetate, washed with water, with a saturated aqueous $NaHCO_3$ solution, brine. The solution is dried over $MgSO_4$, concentrated. The resulting crude product is purified by column chromatography on silica gel eluting with 2%MeOH:CH_2Cl_2. The title compound (1.8 g, 80 % yield) is obtained as a viscous oil.

$C_{36}H_{34}N_4O_3S$ MS $(M+H)^+$: 603

B. 4-Benzyloxycarbonyl-1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one.

To a solution of 4-benzyloxycarbonyl-1- [3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one (1.8 g, 3 mmol) in 20 ml of ethyle acetate is added concentrated hydrochloric acid (10 drops) and H_2O (10 drops). The resulting mixture is stirred for 1 hour, the ethyle acetate solution is decanted, washed with a saturated aqueous $NaHCO_3$ solution, with water, brine. The solution is dried over $MgSO_4$, concentrated. The resulting crude product is purified by column chromatography on silica gel eluting with 1%MeOH:CH_2Cl_2. The title compound (1.17 g, 89% yield) is obtained as a yellow foam.

$C_{23}H_{26}N_4O_3S$ MS $(M+H)^+$: 439

C. 1-(4-Amino-quinazolin-7-ylmethyl)-4-benzyloxycarbonyl-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one.

To a solution of 4-benzyloxycarbonyl-1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one (1.17 g, 2.67 mmol) in 15 ml of ethanol is added 1,3,5-triazine and glacial acetic acid (3.1 ml, 53.4 mmol). The resulting solution is refluxed for 20 hours, concentrated under vacuum. The residue is dissolved in ethyle acetate, washed with 1N hydrochloric acid, a saturated aqueous $NaHCO_3$ solution, water, brine. The solution is dried over $MgSO_4$, concentrated . The resulting crude product is purified by column chromatography eluting with a gradient of 5%MeOH:CH_2Cl_2 to 10%MeOH:CH_2Cl_2. The title compound (489 mg, 39% yield) is obtained as a yellow solid.

$C_{24}H_{27}N_5O_3S$ MS $(M+H)^+$: 466.

D. 1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one.

1-(4-Amino-quinazolin-7-ylmethyl)-4-benzyloxycarbonyl-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one (100 mg, 0.215 mmol) is dissolved in 5 ml of 30% hydrogen bromide in acetic acid. The mixture is stirred for 1 hour, diluted with ethyle ether. The ether is decanted and the resulting solid is washed thoroughly with ethyle ether. The resulting crude product is purified by column chromatography eluting with a 4/2/1 mixture of CH_2Cl_2 /MeOH/ NH_4OH (30% in H_2O). with a gradient of 5%MeOH:CH_2Cl_2 to 10%MeOH:CH_2Cl_2. The resulting product is purified by another column chromatography eluting with a gradient of 20%MeOH:CH_2Cl_2 to 50%MeOH:CH_2Cl_2. The title compound (30 mg, 42 % yield) is obtained as an off-white solid.

$C_{16}H_{25}N_5OS$ MS $(M+H)^+$: 332.

The following compounds are prepared from the templates described above, coupled with an amino-quinazoline group, and the appropriate sulfonyl choride using the method of Example 101.

Example	Name	m/z (M+H)
898	(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isopropyl-piperazin-2-one	513
899	(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isopropyl-piperazin-2-one	530
900	(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isopropyl-piperazin-2-one	514
901	(R/S)1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid ethyl ester	544
902	(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one	515
903	(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isopropyl-piperazin-2-one	514
904	(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isopropyl-piperazin-2-one	513
905	(4aRS,8aSR)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-octahydro-quinoxalin-2-one	542
906	(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one	515, 517 Cl pattern
907	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-piperazin-2-one	471
908	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-piperazin-2-one	471
909	[1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-(S)-yl]-acetic acid	546
910	[1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-(S)-yl]-acetic acid tert-butyl ester	602
911	(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one	516
912	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-	628

	benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid (2-pyrrolidin-1-yl-ethyl)-amide	
913	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid 2-pyrrolidin-1-yl-ethyl ester	629
914	(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-piperazin-2-one	532
915	(s)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-piperazin-2-one	532
916	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-sulfonic acid (4-chloro-phenyl)-amide	491

The following compounds can be prepared from the templates described above, coupled with an amino-quinazoline group, and the appropriate sulfonyl choride using the method of Example 101.

Example	Name
917	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid 2-imidazol-1-yl-ethyl ester
918	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid 2-morpholin-4-yl-ethyl ester
919	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid pyrrolidin-2-ylmethyl ester
920	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid 2-methylamino-ethyl ester
921	(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methyl-piperazin-2-one
922	(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methyl-piperazin-2-one
923	(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isopropyl-piperazin-2-one
924	(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isobutyl-piperazin-2-one
925	(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isobutyl-piperazin-2-one
926	(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-

	6-methyl-piperazin-2-one
927	(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-methyl-piperazin-2-one
928	(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one
929	(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one
930	(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-methyl-piperazin-2-one
931	(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-methyl-piperazin-2-one
932	(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one
933	(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one
934	(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-methyl-piperazin-2-one
935	(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-methyl-piperazin-2-one
936	(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isobutyl-piperazin-2-one
937	(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isobutyl-piperazin-2-one

The following compounds are prepared from the templates described above, coupled with an amino-quinazoline group, and the appropriate alkylating reagent using the method of Example 268.

Example	Name	m/z (M+H)
938	1-(4-Amino-quinazolin-7-ylmethyl)-4-(2-chloro-imidazo[1,2-a]pyridin-7-ylmethyl)-piperazin-2-one	422
939	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-3(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one	495
940	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-(S)-6-methyl-(S)-3-propyl-piperazin-2-one	470, 472 Cl pattern
941	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-thieno[2,3-b]pyridin-2-	481, 483

	ylmethyl)-(S)-3-propyl-piperazin-2-one	Cl pattern
942	2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo(S)--2-propyl-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester	563, 565 Cl pattern
943	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-(S)-3-propyl-piperazin-2-one	463, 465 Cl pattern
944	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzofuran-2-ylmethyl)-3(S)-propyl-piperazin-2-one	464
945	9-(4-Amino-quinazolin-7-ylmethyl)-6-[3-(5-chloro-thiophen-2-yl)-allyl]-6,9-diaza-spiro[4.5]decan-10-one	468
946	(4aRS,8aSR)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-octahydro-quinoxalin-2-one	468,470 Cl pattern
947	(4aRS,8aSR)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-octahydro-quinoxalin-2-one	475, 477 Cl pattern
948	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-3(S)-isobutyl-piperazin-2-one	477, 479 Cl pattern
949	1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3(S)-isobutyl-piperazin-2-one	489, 491 Cl pattern
950	3-[4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazin-1-ylmethyl]-benzamidine	434
951	(4aRS,8aRS)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-octahydro-quinoxalin-2-one	475, 477 Cl pattern
952	(4aRS,8aRS)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-octahydro-quinoxalin-2-one	468, 470 Cl pattern
953	(4aRS,8aRS)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-octahydro-quinoxalin-2-one	487, 489 Cl pattern
954	2-[4-(4-Amino-quinazolin-7-ylmethyl)-1-(7-chloro-isoquinolin-3-ylmethyl)-3-oxo-piperazin-2-(S)-yl]-N-methyl-acetamide	504, 506 Cl pattern
955	2-[4-(4-Amino-quinazolin-7-ylmethyl)-1-(7-chloro-isoquinolin-3-ylmethyl)-3-oxo-piperazin-2-(S)-yl]-acetamide	490, 492 Cl pattern
956	2-{4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(5-chloro-thiophen-2-yl)-allyl]-3-oxo-piperazin-2-(S)-yl}-acetamide	471, 473 Cl pattern
957	2-{4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(5-chloro-thiophen-2-yl)-allyl]-3-oxo-piperazin-2-(S)-yl}-N-methyl-acetamide	485, 487 Cl pattern
958	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-	470, 472

	3(S)-isobutyl-piperazin-2-one	CI pattern
959	(s)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-methoxymethyl-piperazin-2-one	458, 460 CI pattern
960	1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-3(S)-methoxymethyl-piperazin-2-one	465
961	1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-methoxymethyl-4-(4-pyrimidin-4-yl-benzyl)-piperazin-2-one	470
962	4-[4-(2-Amino-pyrimidin-4-yl)-benzyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one	485
963	3-Amino-5-[4-(4-amino-quinazolin-7-ylmethyl)-2(S)-methoxymethyl-3-oxo-piperazin-1-ylmethyl]-thiophene-2-carbonitrile	438
964	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3(S)-(2-methoxy-ethyl)-piperazin-2-one	472

EXAMPLE 965. 3-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazin-1-yl]-3-oxo-propenyl}-benzonitrile.

To a solution of 1-(4-amino-quinazoline-7-ylmethyl)-3-(S)-methoxymethyl-piperazine-2-one, EXAMPLE 75, (50 mg, 0.16 mmol) and 3-cyanocinnamic acid (29 mg, 0.17 mmol, prepared from 3-cyanobenzaldehyde) in 1 mL of DMF is added N,N-diisopropylethylamine (0.07 mL, 0.38 mmol), followed by 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) (59 mg, 0.18 mmol). The resulting mixture is stirred at room temperature for 16 h and the solution is concentrated. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 60% CH_3CN/H_2O (0.1% TFA) over 30 min and the appropriate product fractions are combined and lyopholized to provide the title compound (73 mg, 0.13 mmol) as a white solid. ^1H NMR (d_6-DMSO, 300 MHz) δ 9.72 (bs, 2H), 8.78 (s, 1H), 8.40 (s, 1H), 8.35 (d, 1H), 8.04 (m, 1H), 7.83 (d, 1H), 7.60 (m, 4H), 7.46 (d, 1H), 5.25-4.44 (m, 4H, rotamers), 4.02 (m, 1H), 3.66 (m, 1H), 3.51-3.40 (m, 3H), 3.27 (s, 3H). ISP MS, $[M+H]^+$=457.

EXAMPLE 966. 3-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazin-1-yl]-3-oxo-propenyl}-benzamidine.

3-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazin-1-yl]-3-oxo-propenyl}-benzonitrile (68 mg, 0.12 mmol) is dissolved in 9 mL of 2:1 ethanol/CH_2Cl_2. The solution is cooled to 0°C and HCl gas is bubbled through the solution for 5 min. The ice bath is removed and the reaction mixture is stirred at room temperature overnight. After this time, the

solution is concentrated. The residue is dissolved in 10 mL of methanol. The solution is cooled to 0°C and NH_3 gas is bubbled through the solution for 5 min. The reaction mixture is heated at reflux for 2 h. After this time, the solution is concentrated. The residue is purified by RP-HPLC eluting with a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 60% CH_3CN/H_2O (0.1% TFA) over 30 min. The appropriate fractions are lyophilized to give the title compound (55 mg, 0.08 mmol) as a solid. ^1H NMR (d_6-DMSO, 300 MHz) δ 9.75 (bs, 2H), 9.36 (bs, 4H), 8.80 (s, 1H), 8.42 (s, 1H), 8.13 (m, 1H), 8.10 (m, 1H), 7.79 (d, 1H), 7.62 (m, 4H), 7.42 (m, 1H), 5.20-4.46 (m, 4H, rotamers), 4.03 (m, 1H), 3.86 (m, 1H), 3.56-3.34 (m, 3H), 3.28 (s, 3H). ISP MS, $[M+H]^+$=474.

EXAMPLE 967. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-hydroxy-phenyl)-acryloyl]-(3S)-propyl-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 123 using 4-hydroxy-cinnamic acid and 1-(4-amino-quinazoline-7-ylmethyl)-3-(S)-methoxymethyl-piperazine-2-one (EXAMPLE 75).

^1H NMR (d_6-DMSO, 300 MHz) δ 9.88 (s, 1H), 9.68 (bs, 2H), 8.80 (s, 1H), 8.36 (d, 1H), 7.58 (m, 4H), 7.48 (d, 1H), 7.07 (d, 1H), 6.76 (d, 2H), 5.06-4.41 (m, 3H, rotamers), 3.62-3.25 (m, 4H), 1.87 (m, 2H), 1.32 (m, 2H), 0.89 (t, 3H). ISP MS, $[M+H]^+$=446.

EXAMPLE 968. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-acryloyl]-(3S)-propyl-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 123 using 3-chloro-cinnamic acid and 1-(4-amino-quinazoline-7-ylmethyl)-3-(S)-methoxymethyl-piperazine-2-one (EXAMPLE 75). ^1H NMR (d_6-DMSO, 300 MHz) δ 9.64 (bs, 2H), 8.78 (s, 1H), 8.36 (d, 1H), 7.96 (m, 1H, rotamers), 7.66 (m, 2H), 7.53 (m, 2H), 7.40 (m, 3H), 5.10-4.42 (m, 3H, rotamers), 3.65 (m, 1H), 3.52-3.22 (m, 3H), 1.90 (m, 2H), 1.33 (m, 2H), 0.90 (t, 3H). ISP MS, $[M+H]^+$=464.

EXAMPLE 969. 1-[4-(4-Aminoquinazoline-7-ylmethyl)-3-oxo-2-propyl-piperazine-1-yl]-3-(5-chloro-thiophen-2-yl)-propane-1,3,dione.

The titled compound is prepared by a modification of a procedure published by Witzeman and Nottingham. (J. Org. Chem. 1991, *56*, 1713.). 1-(4-Aminoquinazoline-7-ylmethyl)-3-propyl-piperazine-2-one (0.299 g, 1mmol) and 3-(5-chloro-thiophen-2-yl)-3-oxo-propionic acid tert-butyl ester (0.287 g, 1.1 mmol) are dissolved in 10 ml of pyridine. The flask containing the resulting solution is placed in an oil bath preheated to 125°C. The reaction is heated with stirring under a stream of nitrogen gas for one hour until most of the pyridine had evaporated.

The remaining pyridine is evaporated *in vacuo*. The residue is purified by flash column chromatography eluting with a gradient of 5% CH_3OH/H_2CCl_2 to 10% CH_3OH/H_2CCl_2 to provide the product (0.48 g, 0.98 mmol). The product could be recrystallized from CH_2Cl_2/hexane to yield a yellow solid. M.P. 120-5°C (dec). MS (ion spray) m/z 486, (M+H).

EXAMPLE 970. 1-[4-(4-Aminoquinazoline-7-ylmethyl)-3-oxo-2-propyl-piperazine-1-yl]-3-(5-chloro-thiophen-2-yl)-2-fluoro-propane-1,3,dione.

Prepared by a procedure of Differding and Ofner. (*Synlett* 1991, 187.). A solution of 1-[4-(4-aminoquinazoline-7-ylmethyl)-3-oxo-2-propyl-piperazine-1-yl]-3-(5-chloro-thiophen-2-yl)-propane-1,3,dione (0.486 g, 1 mmol) in 40 ml of THF is added dropwise to an ice cold suspension of NaH (0.16 g of 60% NaH, 4 mmol) and 5 ml of THF. After the mixture had stirred one hour at 0°C, a solution of N-fluorobenzenesulfonimide (Aldrich) (0.378 g, 1.2 mmol) in 10 ml of THF is added dropwise. The reaction is stirred overnight at room temperature before quenching with glacial acetic acid (0.23 ml, 0.240 g, 4 mmol). The volatiles are evaporated in vacuo and the residue purified by flash column chromatography eluting with a gradient of 5% CH_3OH/H_2CCl_2 to 10% CH_3OH/H_2CCl_2 to provide the product as a white solid. The product could be recrystallized from THF/hexane. M.P. 194-6°C. MS (ion spray) m/z 504, (M+H).

EXAMPLE 971. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one.

To a solution of 1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one (100 mg, 0.3 mmol) in 2 ml of DMF is added DIPEA (158 ml, 0.9 mmol) ,TBTU (107 mg, 0.33 mmol) and 5-chlorothiophen-2-yloxyacetic acid (61 mg, 0.32 mmol). The solution is stirred for 20 hours at room temperature, concentrated under vacuum. The product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O(0.1% TFA) to 80% CH_3CN/H_2O(0.1% TFA). The appropriate collected fractions are lyophilized to afford the title compound as a white solid (63 mg, 33 % yield).

$C_{22}H_{24}N_5O_3S_2Cl.CF_3CO_2H$ $(M+H)^+$: 506

EXAMPLE 972. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl-3-(S)-(2-methanesulfinyl-ethyl)-piperazin-2-one.

To a solution of 1-(4-amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one (29 mg, 0.057 mmol) in 1 ml of CH_2Cl_2 is added at 0°C 3-chloroperbenzoic acid (14 mg at 71 %, 0.057 mmol). The resulting mixture is stirred at room temperature for 2 hours, concentrated. The product is purified by RP-HPLC eluting in a gradient

of 10% CH_3CN/H_2O(0.1% TFA) to 80% CH_3CN/H_2O(0.1% TFA). The appropriate collected fractions are lyophilized to afford the title compound as a white solid (10 mg, 27 % yield).
$C_{22}H_{24}N_5O_4S_2Cl.CF_3CO_2H$ $(M+H)^+$: 522

EXAMPLE 973 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl-3-(S)-(2-methanesulfonyl-ethyl)-piperazin-2-one.

To a solution of 1-(4-amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one (29 mg, 0.057 mmol) in 1 ml of CH_2Cl_2 is added at 0°C 3-chloroperbenzoic acid (28 mg at 71 %, 0.114 mmol). The resulting mixture is stirred at room temperature for 2 hours, concentrated. The product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O(0.1% TFA) to 80% CH_3CN/H_2O(0.1% TFA). The appropriate collected fractions are lyophilized to afford the title compound as a white solid (25 mg, 67 % yield).
$C_{22}H_{24}N_5O_5S_2Cl.CF_3CO_2H$ $(M+H)^+$: 538

Using the methods and templates described above, coupled to an amino-quinazoline group, and methods described in EXAMPLE 123, the following compounds are prepared.

Example	Name	m/z (M+H)
974	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-dimethylaminomethyl-piperazin-2-one	449, 451 Cl pattern
975	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzo-[b]thiophene-2-carbonyl)-(3S)-methoxymethyl-piperazin-2-one	496
976	1-(4-Amino-2-methyl-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-propyl-piperazin-2-one	488, 490 Cl pattern
977	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzofuran-2-carbonyl)-(S)-6-methyl-(S)-3-propyl-piperazin-2-one	492, 494 Cl pattern
978	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzofuran-2-carbonyl)-3(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one	510, 512 Cl pattern
979	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chlorobenzo[b]-thiophene-2-carbonyl)-(S)-3-propyl-piperazin-2-one	494, 496 Cl pattern
980	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzo[b]-thiophene-2-carbonyl)-(S)-6-methyl-(S)-3-propyl-piperazin-2-one	508, 510 Cl pattern
981	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]-thiophene-2-carbonyl)-(S)-6-methyl-(S)-3-propyl-piperazin-2-one	508, 510 Cl pattern

982	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-(S)-6-methyl-(S)-3-propyl-piperazin-2-one	484, 486 Cl pattern
983	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-(S)-6-methyl-(S)-3-propyl-piperazin-2-one	488, 490 Cl pattern
984	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-(S)-6-methyl-(S)-3-propyl-piperazin-2-one	484, 486 Cl pattern
985	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-(S)-6-methyl-(S)-3-propyl-piperazin-2-one	488, 490 Cl pattern
986	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzofuran-2-carbonyl)-3(S)-propyl-piperazin-2-one	478, 480 Cl pattern
987	3-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazin-1-yl]-2-oxo-ethyl}-benzamidine	462
988	3-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-2-oxo-ethyl}-benzamidine	418
989	4-[3-(4-Amino-cyclohexyl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-(3S)-propyl-piperazin-2-one	451
990	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-(S)-3-propyl-piperazin-2-one	494, 496 Cl pattern
991	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzofuran-2-carbonyl)-3(S)-propyl-piperazin-2-one trifluoroacetate	478, 480 Cl pattern
992	1-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-2-propyl-piperazin-1-yl]-3-(3-chloro-phenyl)-propane-1,3-dione	480
993	4-[(5-Amino-pyridin-2-yloxy)-acetyl]-1-(4-amino-quinazolin-7-ylmethyl)-(S)-3-methoxymethyl-piperazin-2-one	452
994	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(R)-methoxymethyl-piperazin-2-one	476, 478 Cl pattern
995	3-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-3-oxo-propyl}-benzamidine	432
996	3-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazin-1-yl]-3-oxo-propyl}-benzamidine	476
997	1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-imidazol-1-yl-benzoyl)-3(S)-propyl-piperazin-2-one	470
998	(6-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-methoxymethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-pyridin-3-yl)-carbamic acid tert-butyl	552

	ester	
999	(4aRS,8aSR)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-octahydro-quinoxalin-2-one	486, 488 Cl pattern
1000	(4aRS,8aRS)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-octahydro-quinoxalin-2-one	486, 488 Cl pattern
1001	(4aRS,8aRS)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-octahydro-quinoxalin-2-one	482, 484 Cl pattern
1002	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-6-oxo-1,6-dihydro-pyridin-3-yl)-acryloyl]-(S)-3-propyl-piperazin-2-one	481, 483 Cl pattern
1003	1-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-2-propyl-piperazin-1-yl]-3-(4-hydroxy-phenyl)-propane-1,3-dione	462
1004	2-{4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-oxo-piperazin-2-(S)-yl}-acetamide	485, 487 Cl pattern
1005	2-{4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-oxo-piperazin-2-(S)-yl}-acetamide	485, 487 Cl pattern
1006	2-{4-(4-Amino-quinazolin-7-ylmethyl)-1-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-oxo-piperazin-2-(S)-yl}-acetamide	489, 491 Cl pattern
1007	{4-(4-Amino-quinazolin-7-ylmethyl)-1-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-oxo-piperazin-2-(S)-yl}-acetic acid methyl ester	504, 506 Cl pattern
1008	2-{4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-oxo-piperazin-2-(S)-yl}-N-methyl-acetamide	499, 501 Cl pattern
1009	2-{4-(4-Amino-quinazolin-7-ylmethyl)-1-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-oxo-piperazin-2-(S)-yl}-N-methyl-acetamide	503, 505 Cl pattern
1010	2-{4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-oxo-piperazin-2-(S)-yl}-N-methyl-acetamide	499, 501 Cl pattern
1011	4-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-methoxymethyl-3-oxo-piperazin-1-yl]-3-oxo-propenyl}-benzenesulfonamide	511
1012	N-(5-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazin-1-yl]-3-oxo-propyl}-pyridin-2-yl)-acetamide	492
1013	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-amino-[1,3,4]thiadiazol-2-ylsulfanyl)-acetyl]-(S)-3-propyl-piperazin-2-one	473
1014	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-amino-[1,3,4]thiadiazol-2-ylsulfanyl)-acetyl]-(S)-3-methoxymethyl-piperazin-2-one	475
1015	3-[4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-	448

	piperazine-1-carbonyl]-benzamidine	
1016	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(piperidin-3-yloxy)-acetyl]-piperazin-2-one	399
1017	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-4-hydroxy-phenyl)-(E)-acryloyl]-(3S)-methoxymethyl-piperazin-2-one	482
1018	(3S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-hydroxy-naphthalene-2-carbonyl)-3-propyl-piperazin-2-one	470
1019	(3S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-hydroxy-1H-indole-2-carbonyl)-3-propyl-piperazin-2-one	459
1020	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-hydroxy-phenoxy)-acetyl]-(3S)-methoxymethyl-piperazin-2-one	452
1021	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-hydroxy-phenyl)-acryloyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one	460
1022	N-(5-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-2-(S)-propyl-piperazin-1-yl]-3-oxo-propenyl}-pyridin-2-yl)-acetamide	488
1023	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one	488, 490 Cl pattern
1024	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-phenoxy)-acetyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one	482, 484 Cl pattern
1025	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3,6-bis-methoxymethyl-piperazin-2-one	
1026	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-acryloyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one	478, 480 Cl pattern
1027	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one	484, 486 Cl pattern
1028	4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-(R)-6-methyl-(S)-3-propyl-piperazin-2-one	478
1029	2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-(S)-2-propyl-piperazin-1-yl]-N-(5-chloro-thiophen-2-yl)-2-oxo-acetamide	487, 489 Cl pattern
1030	2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-N-(5-chloro-thiophen-2-yl)-2-oxo-acetamide	445, 447 Cl pattern
1031	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-3-yl)-acryloyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one	484, 490 Cl pattern
1032	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-	484, 490

	acryloyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one	Cl pattern
1033	2-[4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-methoxymethyl-3-oxo-piperazin-1-yl]-N-(5-chloro-thiophen-2-yl)-2-oxo-acetamide	489, 491 Cl pattern
1034	(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-methoxymethyl-piperazin-2-one	476
1035	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3,4-dihydroxy-phenyl)-(E)-acryloyl]-(3S)-methoxymethyl-piperazin-2-one	464
1036	4-[3-(6-Amino-pyridin-3-yl)-propionyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one	450
1037	4-[3-(6-Amino-pyridin-3-yl)-propionyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-propyl-piperazin-2-one	448
1038	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-(S)-hydroxymethyl-piperazin-2-one	458, 460 Cl pattern
1039	N-(5-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-butyl-3-oxo-piperazin-1-yl]-3-oxo-propenyl}-6-methyl-pyridin-2-yl)-acetamide	516
1040	N-(5-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-butyl-3-oxo-piperazin-1-yl]-3-oxo-propenyl}-pyridin-2-yl)-acetamide	502
1041	4-[3-(6-Amino-2-methyl-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-butyl-piperazin-2-one	474
1042	1-[4-(4-Aminoquinazoline-7-ylmethyl)-3-oxo-piperazin-1-yl]-3-(5-chloro-thiophen-2-yl)-propane-1,3,dione	444
1043	4-[3-(3-Amino-4-chloro-phenyl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-(3S)-methoxymethyl-piperazin-2-one	481
1044	4-[3-(3-Amino-5-chloro-phenyl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-(3S)-methoxymethyl-piperazin-2-one	481
1045	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one	488, 490 Cl pattern
1046	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-thiophen-2-yloxy)-acetyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one	488, 490 Cl pattern
1047	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-benzenesulfinyl)-acetyl]-(3-S)-propyl-piperazin-2-one	500
1048	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-hydroxy-phenoxy)-acetyl]-(3S)-methoxymethyl-piperazin-2-one	452
1049	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-phenylsulfanyl)-	442

	acetyl]-piperazin-2-one	
1050	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-benzenesulfinyl)-acetyl]-(3S)-methoxymethyl-piperazin-2-one	502
1051	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-hydroxy-phenyl)-(E)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one	448
1052	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-hydroxy-phenyl)-(E)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one	448
1053	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-hydroxymethyl-piperazin-2-one	462, 464 Cl pattern
1054	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-hydroxymethyl-piperazin-2-one	458, 460 Cl pattern
1055	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3,6-bis-methoxymethyl-piperazin-2-one	521
1056	(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-methoxymethyl-piperazin-2-one	476
1057	4-[(6-Amino-pyrimidin-4-yloxy)-acetyl]-1-(4-amino-quinazolin-7-ylmethyl)-3(S)-methoxymethyl-piperazin-2-one	453
1058	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-benzenesulfonyl)-acetyl]-piperazin-2-one	474
1059	1-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-3-(4-chloro-phenyl)-propane-1,3-dione	438
1060	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-phenylsulfanyl)-acetyl]-piperazin-2-one	442
1061	4-[3-(6-Amino-2-methyl-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-propyl-piperazin-2-one	460
1062	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-3-hydroxy-acryloyl]-piperazin-2-one	438
1063	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-dimethylamino-phenyl)-acryloyl]-(3S)-propyl-piperazin-2-one	473
1064	3-(S)-6-(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-hydroxymethyl-3-methoxymethyl-piperazin-2-one	506
1065	4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3(S)-isobutyl-piperazin-2-one	460
1066	4-[3-(2-Amino-pyrimidin-5-yl)-acryloyl]-1-(4-amino-quinazolin-7-	447

	ylmethyl)-3(S)-propyl-piperazin-2-one	
1067	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-hydroxy-phenyl)-acryloyl]-(3S)-propyl-piperazin-2-one	446
1068	4-[3-(3-Amino-phenyl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-(3S)-methoxymethyl-piperazin-2-one	447
1069	4-[3-(4-Amino-3-chloro-phenyl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-(3S)-methoxymethyl-piperazin-2-one	481
1070	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-pyrazin-2-yloxy)-acetyl]-(S)-3-methoxymethyl-piperazin-2-one	472, 474 Cl pattern
1071	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-pyrazin-2-yloxy)-acetyl]-(S)-3-propyl-piperazin-2-one	470, 472 Cl pattern
1072	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3(S)-isobutyl-piperazin-2-one	484, 486 Cl pattern
1073	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3(S)-isobutyl-piperazin-2-one	488, 490 Cl pattern
1074	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2-amino-thiazol-4-yl)-acetyl]-(S)-3-propyl-piperazin-2-one	440
1075	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid ethyl ester	504, 506 Cl pattern
1076	4-[3-(4-Amino-phenyl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-(3S)-propyl-piperazin-2-one	445
1077	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3,4-dichloro-thiophen-2-yloxy)-acetyl]-(S)-3-propyl-piperazin-2-one	508, 510, 512 Cl_2 pattern
1078	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3,4-dichloro-thiophen-2-yloxy)-acetyl]-(S)-3-methoxymethyl-piperazin-2-one	510, 512, 514 Cl_2 pattern
1079	4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3(S)-(2-methoxy-ethyl)-piperazin-2-one	462
1080	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3(S)-(2-methoxy-ethyl)-piperazin-2-one	486, 488 Cl pattern
1081	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3(S)-(2-methoxy-ethyl)-piperazin-2-one	486, 488 Cl pattern

EXAMPLE 1082. 4-(4-Amino-quinazolin-7-ylmethyl)-(S)-5-methyl-3-oxo-(S)-2-propyl-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide.

To a solution of 4-[4-Amino-quinazolin-7-ylmethyl]-5-methyl-3-oxo-2-propyl-piperazine (12 mg, 0.04 mmol, EXAMPLE 888) in 2 mL of DMF is added 4-chlorophenyl isocyanate (9 mg, 0.06 mmol). After stirring at 100 °C for 1h , the solution is concentrated. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 70% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions are combined and lyophilized to provide the title compound (16 mg, 0.03 mmol) as a white solid. ^1H NMR (d_6-DMSO, 300 MHz) δ 9.74 (bs, 2H), 8.77 (m, 2H), 8.35 (m, 1H), 7.56 (m, 2H), 7.46 (d, 2H), 7.21 (d, 2H), 5.00-4.38 (m, 3H, rotamers), 4.20 (m, 1H, rotamers), 3.58 (m, 1H, rotamers), 3.10 (m, 1H), 1.86 (m, 2H), 1.33 (m, 2H), 1.08 (m, 3H, rotamers), 0.90 (t, 3H). ISP MS, $[M+H]^+$=467, 469 (Cl pattern).

EXAMPLE 1083. 4-(4-Amino-quinazolin-7-ylmethyl)-(S)-5-methyl-3-oxo-(S)-2-propyl-piperazine-1-carboxylic acid (5-chloro-thiophen-2-yl)amide.

A mixture of 5-chloro-thiophene-2-carbonyl azide (28 mg, 0.15 mmol, EXAMPLE 38) and 4-[4-Amino-quinazolin-7-ylmethyl]-5-methyl-3-oxo-2-propyl-piperazine, EXAMPLE 888, (26 mg, 0.08 mmol) in 3 mL of dry DMF is heated at 100 °C for 1 h. The resulting mixture is concentrated in vacuo. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 70% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions are combined and lyophilized to provide the title compound (18 mg, 0.03 mmol) as a white solid. ^1H NMR (d_6-DMSO, 300 MHz) δ 9.96 (bs, 1H), 9.70 (bs, 2H), 8.72 (s, 1H), 8.22 (d, 1H), 7.55 (d, 1H), 7.50 (s, 1H), 6.68 (d, 1H), 6.37 (d, 1H), 4.99-4.38 (m, 3H, rotamers), 4.15 (m, 1H, rotamers), 3.58 (m, 1H, rotamers), 3.10 (m, 1H), 1.85 (m, 2H), 1.32 (m, 2H), 1.07 (m, 3H, rotamers), 0.88 (t, 3H). ISP MS, $[M+H]^+$=473, 475 (Cl pattern).

Using the above procedures and templates described above, coupled with an amino-quinazoline, the following EXAMPLES are prepared;

Example	Name	m/z (M+H)
1084	4-(4-Amino-quinazolin-7-ylmethyl)-2(S)-isobutyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	466
1085	4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-hydroxymethyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	440
1086	(2S)-4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-2-propyl-piperazine-1-carboxylic acid (5-bromo-thiazol-2-yl)-amide	504

1087	(2S)-4-(4-Amino-quinazolin-7-ylmethyl)-2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-chloro-thiazol-2-yl)-amide	462
1088	(2S)-4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-2-propyl-piperazine-1-carboxylic acid (5-chloro-thiazol-2-yl)-amide	460
1089	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-hydroxy-phenyl)-amide	437
1090	4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methylcarbamoylmethyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	481
1091	4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-carbamoylmethyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	467
1092	(4aRS,8aRS)-4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-octahydro-quinoxaline-1-carboxylic acid (4-chloro-phenyl)-amide	465
1093	4-(4-Amino-quinazolin-7-ylmethyl)-2(S)-(2-methylsulfanyl-ethyl)-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	485, 487 Cl pattern
1094	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-chloro-furan-2-yl)-amide	445
1095	(2S)-4-(4-Amino-quinazolin-7-ylmethyl)-2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-bromo-thiazol-2-yl)-amide	506
1096	N-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-(S)-2-propyl-piperazine-1-carbonyl]-4-chloro-benzenesulfonamide	517, 519 Cl pattern

Using the templates described above with and amino-quinoline or an amino-cinnoline and the methods described in EXAMPLES 718-721;

Example	Name	m/z (M+H)
1097	1-(S)-4-(4-Amino-quinolin-7-ylmethyl)-3-oxo-2-propyl-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	452
1098	1-(S)-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-propyl-piperazin-2-one,	455
1099	1-(S)-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-4-oxy-3-propyl-piperazin-2-one	471
1100	1-(S)-4-(4-Amino-quinolin-7-ylmethyl)-2-methoxymethyl-3-oxo-2-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	425
1101	(S)-4-(4-Aminoquinolin-7-ylmethyl)-2-methoxylmethyl-3-oxo-2-piperazine-1-carboxylic acid (5-chlorothiophen-2-yl)-amide	460
1102	1-(S)-4-(4-Amino-quinolin-7-ylmethyl)-2-methyl-3-oxo-2-piperazine-	390

	1-carboxylic acid phenylamide	
1103	1-(S)-4-(4-Amino-quinolin-7-ylmethyl)-2-methyl-3-oxo-2-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	454
1104	1-(S)-4-(4-Amino-cinnolin-7-ylmethyl)-2-methyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,	425
1105	1-(S)-(4-Amino-cinnolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-methyl-piperazin-2-one,	442
1106	1-(4-Amino-cinnolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-methyl-piperazin-2-one	428

The following compounds are prepared using the methods described above using the appropriate ketopiperazine and sulfonyl chloride. The racemates are separated on a CHIRALPAK AD 10 □m column.

Example	Name	m/z (M+H)
1107	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(+)-carboxylic acid methyl ester	598, 600, Cl pattern
1108	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(-)-carboxylic acid methyl ester	598, 600, Cl pattern
1109	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(+)-carboxylic acid amide	504, 506, Cl pattern
1110	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(-)-carboxylic acid amide	504, 506, Cl pattern
1111	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	481, 483, Cl pattern
1112	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	505, 507, Cl pattern
1113	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-hydroxymethyl-1-(1-methyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	481, 483 Cl pattern
1114	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-hydroxymethyl-1-(1-methyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	505, 507 Cl pattern
1115	4-(5-Chloro-1H-indole-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	444
1116	4-(5-Chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-1-(1H-	488, 490

	pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	CI pattern
1117	4-(7-Methoxy-naphthalene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	451
1118	4-(Benzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	427

Representative Syntheses of Alkyl Azaindoles:

Example 1119 4-[4-(5-Chloro-thiophen-2-yl)-benzyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one

A. 4-(5-Chloro-thiophen-2-yl)-benzaldehyde

4-Formylphenylboronic acid (1.37 g, 9.15 mmol), 2-bromo-5-chlorothiophene (1 mL, 9.15 mmol), 2M Na_2CO_3 (9 mL, 18.3 mmol) and $Pd(PPh_3)_4$ (0.53 mg, 0.46 mmol) in DME (30 mL) are heated to reflux for 4 h after which time the reaction mixture is concentrated in vacuo and taken up in EtOAc. The organic solution is washed with water (x2) then brine and dried over $MgSO_4$, filtered and concentrated to dryness. The crude residue is purified by chromatography using 5% EtOAc/hexanes as the eluent to yield a yellow solid (1.8 g, 8.1 mmol) as the title compound. EI MS $[M^{\cdot}]$+= 222, 224, CI pattern.

B. 2-{4-[4-(5-Chloro-thiophen-2-yl)-benzyl]-2-oxo-piperazin-1-ylmethyl}-pyrrolo[3,2-c]pyridine-1-carboxylic acid *tert*-butyl ester

To a solution of 2-(2-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid *tert*-butyl ester (0.10 g, 0.30 mmol) in acetonitrile (5 mL) is added 4-(5-chloro-thiophen-2-yl)-benzaldehyde (0.067 g, 0.30 mmol) followed by triacetoxyborohydride (0.13 g, 0.60 mmol) and glacial acetic acid (1 drop). The resulting mixture is stirred at room temperature overnight then poured into EtOAc and washed with water (x2) and brine. The organic layer is dried over $MgSO_4$, filtered and concentrated to dryness then purified by column chromatography using EtOAc as the eluent to yield the title compound (0.90 g, 0.17 mmol). ESI MS [M+H]+= 537.

C. 4-[4-(5-Chloro-thiophen-2-yl)-benzyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one

2-{4-[4-(5-Chloro-thiophen-2-yl)-benzyl]-2-oxo-piperazin-1-ylmethyl}-pyrrolo[3,2-c]pyridine-1-carboxylic acid *tert*-butyl ester (0.90 g, 0.17 mmol) is stirred in 30% TFA/CH_2Cl_2 (8 mL) for 1 h then concentratated to dryness and purified by RP-HPLC using 10-100% acetonitrile/0.1% TFA water as the eluent. The appropriate fractions are collected and lypholized to yield the title product as an amorphous white solid (0.44 mg, 0.08 mmol).

Example	Name	m/z (M+H)
1120	4-[3-(5-Chloro-thiophen-2-yl)-benzyl]-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	479

1121	4-[3-(5-Chloro-thiophen-2-yl)-benzyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	437
1122	4-[5-(5-Chloro-thiophen-2-yl)-pyridin-2-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	438
1123	4-[5-(5-Chloro-thiophen-2-yl)-pyridin-2-ylmethyl]-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	480
1124	4-[5-(5-Chloro-thiophen-2-yl)-pyridin-2-ylmethyl]-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	482
1125	4-[2-(4-Chloro-phenyl)-1H-indol-3-ylmethyl]-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	512
1126	4-[6-(5-Chloro-thiophen-2-yl)-pyridin-2-ylmethyl]-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	482
1127	4-[4-(5-Chloro-thiophen-2-yl)-benzyl]-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	481
1128	4-[6-(5-Chloro-thiophen-2-yl)-pyridin-2-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	438
1129	4-(5-Chloro-[2,3']bithiophenyl-5'-ylmethyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	443
1130	4-(5'-Chloro-[2,2']bithiophenyl-5-ylmethyl)-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	487
1131	4-[2,2']Bithiophenyl-5-ylmethyl-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	453
1132	4-(5-Chloro-[2,3']bithiophenyl-5'-ylmethyl)-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	485
1133	4-[6-(5-Chloro-thiophen-2-yl)-pyridin-2-ylmethyl]-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	480
1134	4-[3-(5-Chloro-thiophen-2-yl)-4-fluoro-benzyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	455
1135	4-[5-(3-Chloro-phenyl)-furan-2-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	421
1136	4-[4-(5-Chloro-thiophen-2-yl)-benzyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	437
1137	4-[3-(5-Chloro-thiophen-2-yl)-4-fluoro-benzyl]-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	497

1138	4-[4-(5-Chloro-thiophen-2-yl)-benzyl]-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	479
1139	4-[5-(3-Chloro-phenyl)-furan-2-ylmethyl]-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	463
1140	4-[3-(5-Chloro-thiophen-2-yl)-allyl]-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	429,431 Cl pattern
1141	4-(5-Chloro-1H-indol-2-ylmethyl)-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	436
1142	4-(5'-Chloro-[2,2']bithiophenyl-5-ylmethyl)-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	485, 487 Cl pattern
1143	4-[4-(5-Chloro-thiophen-2-yl)-benzyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	481
1144	4-[5-(5-Chloro-thiophen-2-yl)-pyridin-2-ylmethyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	482

The following compounds are prepared using the templates described above coupled with an amino-methyl-quinazoline, a quinazolinone, hydroxy-quinoline, an oxo-1,6-dihydro-pyridin-benzyl, a 6-methoxy-pyridin-3-yl)-benzyl or 3-imidazol-1-yl-benzyl group using the methods described in EXAMPLE 860 and the sulfonylation, alkylation or amide coupling reactions described above.

Example	Name	m/z (M+H)
1145	1-(4-Amino-2-methyl-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-propyl-piperazin-2-one	487
1146	7-{4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-2-oxo-(S)-3-propyl-piperazin-1-ylmethyl}-3H-quinazolin-4-one	471, 473 Cl pattern
1147	7-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-2-oxo-(S)-3-propyl-piperazin-1-ylmethyl}-3H-quinazolin-4-one	475, 477 Cl pattern
1148	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-(S)-6-methyl-(S)-3-propyl-piperazin-2-one	484, 486 Cl pattern
1149	4-[3-(5-Chloro-thiophen-2-yl)-allyl]-(S)-3-ethyl-1-(4-hydroxy-quinolin-7-ylmethyl)-piperazin-2-one	442, 444, Cl pattern
1150	7-{4-[3-(5-Chloro-thiophen-2-yl)-allyl]-3-(S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-2H-isoquinolin-1-one	457
1151	7-[4-(7-Chloro-isoquinolin-3-ylmethyl)-3-(S)-methoxymethyl-2-oxo-	477, 479

	piperazin-1-ylmethyl]-2H-isoquinolin-1-one	Cl pattern
1152	4-(5-Chloro-1H-indol-2-ylmethyl)-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one	489, 491 Cl pattern
1153	4-(5-Chloro-1H-indol-2-ylmethyl)-3-(S)-methyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one	561, 563 Cl pattern
1154	6-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-3-methyl-3H-quinazolin-4-one	491, 493 Cl pattern
1155	6-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-3H-quinazolin-4-one	477, 479 Cl pattern
1156	4-(7-Chloro-isoquinolin-3-ylmethyl)-3-(S)-methyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one	473, 475 Cl pattern
1157	4-(7-Chloro-isoquinolin-3-ylmethyl)-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one	459, 461 Cl pattern
1158	4-(7-Chloro-isoquinolin-3-ylmethyl)-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-(S)-methyl-piperazin-2-one	487, 489 Cl pattern
1159	4-(7-Chloro-isoquinolin-3-ylmethyl)-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one	501, 503 Cl pattern
1160	4-(7-Chloro-isoquinolin-3-ylmethyl)-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-piperazin-2-one	473, 475 Cl pattern
1161	4-(7-Chloro-isoquinolin-3-ylmethyl)-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one	515, 517 Cl pattern
1162	4-(7-Chloro-isoquinolin-3-ylmethyl)-3-(S)-methoxymethyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one	503
1163	4-[3-(6-Amino-pyridin-3-yl)-propionyl]-3-(S)-methoxymethyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one	476
1164	(S)-4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-6-methoxymethyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-piperazin-2-one	516
1165	4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-3(S)-isobutyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one	510
1166	4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-(3-imidazol-1-yl-benzyl)-3-(S)-methoxymethyl-piperazin-2-one	475, 477 Cl pattern
1167	4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3(S)-isobutyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one	514
1168	4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-3(S)-isobutyl-1-[4-(6-oxo-1,6-	486

	dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one	
1169	4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one	472
1170	4-[(5-Chloro-thiophen-3-yloxy)-acetyl]-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one	500, 502 Cl pattern
1171	4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one	500, 502 Cl pattern
1172	4-[3-(4-Chloro-thiophen-2-yl)-acryloyl]-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one	496, 498 Cl pattern
1173	4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one	496, 498 Cl pattern
1174	4-[3-(4-Chloro-thiophen-2-yl)-acryloyl]-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one	510, 512 Cl pattern
1175	4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one	514, 516 Cl pattern
1176	4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one	510, 512 Cl pattern
1177	4-[(5-Chloro-thiophen-3-yloxy)-acetyl]-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one	514, 516 Cl pattern

EXAMPLE 1178 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-6,7-dihydro-5H-benzothiazol-4-one.

A: 4-Cyanomethyl-piperazine-1-carboxylic acid tert-butyl ester

To a partially dissolved solution of piperazine-1-carboxylic acid tert-butyl ester (2.0 g, 10 mmol) in THF (30 mL) is added 60% NaH (0.44 g, 11 mmol). The resulting solution is stirred for 5 min before the addition of bromoacetonitrile (0.9 mL, 13 mmol). The reaction is stirred for 4 h. MeOH (1 mL) is added and the solution is concentrated and the residue is diluted with EtOAc, washed with 1 N HCl, H_2O, $NaHCO_3$ and the solution is dried over $MgSO_4$. The filtrate is concentrated and the crude product is chromatographed using a silica column (50% EtOAc/PE - EtOAc) to yield 4-cyanomethyl-piperazine-1-carboxylic acid tert-butyl ester. ^1H NMR (300 MHz, $CDCl_3$) δ 4.41 (s, 2H), 4.16 (s, 2H), 3.75 (t, 2H), 3.51 (t, 2H), 1.47 (s, 9H).

B: Piperazin-1-yl-acetonitrile

To a solution of 30% TFA/CH_2Cl_2 (10 mL) is added 4-cyanomethyl-piperazine-1-carboxylic acid tert-butyl ester (1.7 g, 6.8 mmol) and the reaction is stirred for 14 h. The reaction is concentrated and chromatoghraphed using silica gel (%1 NH_4OH/7% MeOH/ CH_2Cl_2) to isolate

piperazin-1-yl-acetonitrile as the free base. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36 (s, 2H), 3.54 (s, 2H), 3.45 (t, 2H), 3.13 (t, 2H).

C: [4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-1-yl]-acetonitrile

To a solution of piperazin-1-yl-acetonitrile (0.32 g, 2.3 mmol) and Et_3N (350 mg, 3.4 mmol) is added 6-chloro-benzo[b]thiophene-2-sulfonyl chloride (615 mg, 2.3 mmol) at 0 °C. The reaction is warmed to room temperature and stirred 4 h. The reaction is diluted with CH_2Cl_2, washed with 1 N HCl, $NaHCO_3$ and dried over $MgSO_4$. The solution is concentrated and the residue is triturated with PE, triturated with Et_2O, and pumped to yield [4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-1-yl]-acetonitrile which can be used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89-7.84 (m, 3H), 7.48 (dd, 1H), 4.36 (s, 2H), 3.92 (s, 2H), 3.64-3.61 (m, 2H), 3.57-3.54 (m, 2H); MS (Ion Spray) 444 $(M+H)^+$.

D: 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-1-yl]-thioacetamide

A suspension of [4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-1-yl]-acetonitrile (1.2 g, 3.2 mmol) is heated with diisopropylethylamine (0.65 g, 5.0 mmol) in a solution of ethanol saturated with hydrogen sulfide gas for 4 hours. The reaction is cooled, filtered and washed with cold ethanol to provide 2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-1-yl]-thioacetamide. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.71 (bs, 1H), 9.01 (bs, 1H), 8.35 (d, 1H), 8.21 (s, 1H), 8.08 (d, 1H), 7.59 (dd, 1H), 4.15 (s, 2H), 3.73 (s, 2H), 3.43 (s, 4H).

E: 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-6,7-dihydro-5H-benzothiazol-4-one

To a solution of toluene/t-butanol (1:1) is added 2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-1-yl]-thioacetamide (180 mg, 0.45 mmol) and 3-bromo-cyclohexane-1,2-dione (135 mg, 0.80 mmol). The reaction is heated at 90 °C for 4 h and is then concentrated and crude product is dissolved in CH_2Cl_2 and washed with $NaHCO_3$. The solution is concentrated and purified using 1% MeOH/EtOAc to provide 2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-6,7-dihydro-5H-benzothiazol-4-one. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.82 (m, 3H), 7.47 (dd, 1H), 4.80 (s, 2H), 3.91 (s, 2H), 3.61 (t, 2H), 3.43 (t, 2H), 3.05 (t, 2H), 2.65 (t, 2H), 2.24 (dt, 2H); MS (Ion Spray) 496 $(M+H)^+$.

Using the corresponding α-haloketones, the following products can be produced:

EXAMPLE 1179 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4-methyl-thiazole-5-carboxylic acid methylamide.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.82 (m, 3H), 7.46 (dd, 1H), 5.69 (br, 1H), 4.74 (s, 2H), 3.91 (s, 2H), 3.63-3.59 (m, 2H), 3.49-3.43 (m, 2H), 2.94 (d, 3H), 2.61 (s, 3H); MS (Ion Spray) 499 $(M+H)^+$.

EXAMPLE 1180 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4-methyl-thiazole-5-carboxylic acid dimethylamide.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88-7.82 (m, 3H), 7.46 (dd, 1H), 4.76 (s, 2H), 3.90 (s, 2H), 3.62-3.59 (m, 2H), 3.46-3.42 (m, 2H), 3.03 (br, 6H), 2.37 (s, 3H); MS (Ion Spray) 513 $(M+H)^+$.

EXAMPLE 1181 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-pyridin-4-yl-thiazol-2-ylmethyl)-piperazin-2-one hydrobromide.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (br, 2H), 7.83-7.80 (m, 3H), 7.77 (br, 2H), 7.66 (s, 1H), 7.44 (dd, 1H), 4.87 (s, 2H), 3.96 (s, 2H), 3.70-3.66 (m, 2H), 3.52-3.49 (m, 2H); MS (Ion Spray) 505 $(M+H)^+$.

EXAMPLE 1182 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid amide.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.82 (m, 3H), 7.46 (dd, 1H), 6.84 (br, 1H), 5.60 (br, 1H), 4.85 (d, 1H), 4.66 (d, 1H), 3.91 (s, 2H), 3.64-3.52 (m, 3H), 3.47-3.44 (m, 2H), 2.76-2.62 (m, 2H), 2.41-2.33 (m, 1H), 1.93-2.81 (m, 3H); MS (Ion Spray) 525 $(M+H)^+$.

EXAMPLE 1183 {2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-acetic acid methyl ester.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86-7.82 (m, 3H), 7.46 (dd, 1H), 7.11 (s, 1H), 4.80 (s, 2H), 3.93 (s, 2H), 3.78 (s, 2H), 3.73 (s, 3H), 3.61-3.57 (m, 2H), 3.47-3.44 (m, 2H); MS (Ion Spray) 500 $(M+H)^+$.

EXAMPLE 1184 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid ethyl ester.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.86-7.81 (m, 3H), 7.46 (dd, 1H), 4.86 (s, 2H), 4.41 (q, 2H), 3.93 (s, 2H), 3.63-3.59 (m, 2H), 3.48-3.44 (m, 2H), 1.39 (t, 3H); MS (Ion Spray) 500 $(M+H)^+$.

EXAMPLE 1185 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4-methyl-thiazole-5-carboxylic acid methyl ester.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.83 (m, 3H), 7.47 (dd, 1H), 4.76 (s, 2H), 3.93 (s, 2H), 3.84 (s, 3H), 3.64-3.60 (m, 2H), 3.49-3.45 (m, 2H) 2.66 (s, 3H); MS (Ion Spray) 500 $(M+H)^+$.

EXAMPLE 1186 1-(4-tert-Butyl-thiazol-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.82 (m, 3H), 7.46 (dd, 1H), 6.79 (s, 1H), 4.81 (s, 2H), 3.93 (s, 2H), 3.61-3.58 (m, 2H), 3.48-3.44 (m, 2H), 1.29 (s, 9H); MS (Ion Spray) 484 $(M+H)^+$.

EXAMPLE 1187 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[4-(5-chloro-thiophen-2-yl)-thiazol-2-ylmethyl]-piperazin-2-one.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83-7.81 (m, 3H), 7.45 (dd, 1H), 7.18 (s, 1H), 7.13 (d, 1H), 6.86 (d, 1H), 4.81 (s, 2H), 3.95 (s, 2H), 3.67-3.64 (m, 2H), 3.52-3.48 (m, 2H); MS (Ion Spray) 544 $(M+H)^+$.

EXAMPLE 1188 1-[4-(4-Bromo-phenyl)-thiazol-2-ylmethyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83-7.80 (m, 3H), 7.70 (ddd, 2H), 7.53 (ddd, 2H), 7.45 (dd, 1H), 7.38 (s, 1H), 4.86 (s, 2H), 3.96 (s, 2H), 3.68-3.65 (m, 2H), 3.51-3.48 (m, 2H); MS (Ion Spray) 582 $(M+H)^+$.

EXAMPLE 1188 1-[4-(3-Bromo-phenyl)-thiazol-2-ylmethyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (dd, 1H), 7.83-7.80 (m, 3H), 7.73 (dd, 1H), 7.48-7.40 (m, 3H), 7.28 (dd, 1H), 4.86 (s, 2H), 3.96 (s, 2H), 3.69-3.65 (m, 2H), 3.52-3.48 (m, 2H); MS (Ion Spray) 582 $(M+H)^+$.

EXAMPLE 1189 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-methyl-thiazol-2-ylmethyl)-piperazin-2-one.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85-7.80 (m, 3H), 7.45 (dd, 1H), 6.79 (s, 1H), 4.78 (s, 2H), 3.92 (s, 2H), 3.59-3.56 (m, 2H), 3.47-3.43 (m, 2H) 2.38 (s, 3H); MS (Ion Spray) 442 $(M+H)^+$.

EXAMPLE 1190 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-pyridin-3-yl-thiazol-2-ylmethyl)-piperazin-2-one

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.07 (dd, 1H), 8.58 (dd, 1H), 8.11 (ddd, 1H), 7.83-7.79 (m, 3H), 7.43 (dd, 1H), 7.33 (dd, 1H), 4.86 (s, 2H), 3.95 (s, 2H), 3.67-3.64 (m, 2H), 3.51-3.47 (m, 2H); MS (Ion Spray) 505 $(M+H)^+$.

EXAMPLE 1191 1-(5-Acetyl-4-methyl-thiazol-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86-7.82 (m, 3H), 7.45 (dd, 1H), 4.75 (s, 2H), 3.92 (s, 2H), 3.65-3.61 (m, 2H), 3.48-3.45 (m, 2H), 2.65 (s, 3H), 2.61 (s, 3H); MS (Ion Spray) 499 $(M+H)^+$.

EXAMPLE 1192 3-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-3-methyl-butyric acid ethyl ester.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.82 (m, 3H), 7.46 (dd, 1H), 6.85 (s, 1H), 4.80 (s, 2H), 3.98 (q, 2H), 3.92 (s, 2H), 3.60-3.57 (m, 2H), 3.46-3.43 (m, 2H), 2.66 (s, 2H), 1.40 (s, 6H), 1.12 (t, 3H); MS (Ion Spray) 556 $(M+H)^+$.

EXAMPLE 1193 1-(4-Adamantan-1-yl-thiazol-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86-7.82 (m, 3H), 7.46 (dd, 1H), 6.74 (s, 1H), 4.81 (s, 2H), 3.93 (s, 2H), 3.60-3.57 (m, 2H), 3.48-3.44 (m, 2H), 2.05 (m, 3H), 1.90 (m, 6H), 1.80-1.71 (m, 6H); MS (Ion Spray) 562 $(M+H)^+$.

EXAMPLE 1194 1-(4-Adamantan-1-yl-thiazol-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86-7.82 (m, 3H), 7.46 (dd, 1H), 6.74 (s, 1H), 4.81 (s, 2H), 3.93 (s, 2H), 3.60-3.57 (m, 2H), 3.48-3.44 (m, 2H), 2.05 (m, 3H), 1.90 (m, 6H), 1.80-1.71 (m, 6H); MS (Ion Spray) 562 $(M+H)^+$.

EXAMPLE 1195 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-phenyl-thiazol-2-ylmethyl)-piperazin-2-one.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83-7.79 (m, 5H), 7.45-7.31 (m, 5H), 4.87 (s, 2H), 3.95 (s, 2H), 3.69-3.65 (m, 2H), 3.51-3.47 (m, 2H); MS (Ion Spray) 504 $(M+H)^+$.

EXAMPLE 1195 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[4-(4-hydroxy-phenyl)-thiazol-2-ylmethyl]-piperazin-2-one.

^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD) δ 7.80-7.78 (m, 3H), 7.63 (ddd, 2H), 7.41 (dd, 1H), 7.17 (s, 1H), 6.83 (ddd, 1H), 4.81 (s, 2H), 3.92 (s, 2H), 3.68-3.61 (m, 2H), 3.48-3.44 (m, 2H); MS (Ion Spray) 520 $(M+H)^+$.

EXAMPLE 1196 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[4-(4-hydroxy-phenyl)-thiazol-2-ylmethyl]-piperazin-2-one.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82-7.79 (m, 3H), 7.43 (dd, 1H), 7.36-7.34 (md, 3H), 7.25 (m, 1H), 6.83 (dd, 1H), 6.10 (br, 1H), 4.86 (s, 2H), 3.95 (s, 2H), 3.68-3.64 (m, 2H), 3.50-3.47 (m, 2H); MS (Ion Spray) 520 $(M+H)^+$.

EXAMPLE 1197 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4,5,6,7-tetrahydro-benzothiazol-2-ylmethyl)-piperazin-2-one.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.82 (m, 3H), 7.46 (dd, 1H), 4.80 (s, 2H), 3.91 (s, 2H), 3.61-3.58 (m, 2H), 3.46-3.43 (m, 2H), 2.72 (bm, 4H), 1.83 (bs, 4H); MS (Ion Spray) 482 $(M+H)^+$.

EXAMPLE 1198 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid dimethylamide

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.77 (m, 4H), 7.47 (dd, 1H), 4.83 (s, 2H), 3.92 (s, 2H), 3.63-3.60 (m, 2H), 3.47-3.43 (m, 2H), 3.18 (s, 3H), 3.10 (s, 3H); MS (Ion Spray) 499 $(M+H)^+$.

EXAMPLE 1199 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid ethyl ester

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.81 (m, 3H), 7.46 (dd, 1H), 4.81 (s, 2H), 4.17 (q, 2H), 3.91 (s, 1H), 3.89 (s, 1H), 3.80 (t, 0.5), 3.60-2.52 (m, 2.5H), 3.45-3.36 (m, 2H), 2.78-2.68 (m, 2H), 2.16-1.77 (m, 4H), 1.25 (t, 3H); MS (Ion Spray) 554 $(M+H)^+$.

EXAMPLE 1200 2-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-benzoic acid

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, 1H), 7.80-7.76 (m, 3H), 7.55-7.35 (m, 5H), (s, 2H), 3.94 (s, 2H), 3.55 (m, 2H), 3.43 (m, 2H); MS (ion spray) 548 $(M+H)^+$.

EXAMPLE 1201 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[4-(2-hydroxy-phenyl)-thiazol-2-ylmethyl]-piperazin-2-one

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.2 (s, 1H), 7.82-7.79 (m, 3H), 7.55 (dd, 1H), 7.45-7.40 (m, 2H), 7.24 (d, 1H), 6.97-6.89 (m, 2H), 4.87 (s, 2H), 3.95 (s, 2H), 3.61 (m, 2H), 3.50 (m, 2H); MS (ion spray) 520 $(M+H)^+$.

EXAMPLE 1202 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-pyridin-2-yl-thiazol-2-ylmethyl)-piperazin-2-one

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.99 (d, 1H), 7.96 (s, 1H), 7.83-7.74 (m, 4H), 7.43 (dd, 1H), 7.23-7.19 (m, 1H), 4.88 (s, 2H), 3.94 (s, 2H), 3.65 (m, 2H), 3.48 (m, 2H); MS (ion spray) 505 $(M+H)^+$.

EXAMPLE 1203 2-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-benzamide

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.84-7.79 (m, 2H), 7.61-7.55 (m, 2H), 7.48-7.37 (m, 4 H), 5.86 (d (broad), 2H), 4.83 (s, 2H), 3.92 (s, 2H), 3.65 (m, 2H), 3.47 (m, 2H)
MS (ion spray) 547 $(M+H)^+$.

Using procedures described above the following compounds can be made;

EXAMPLE 1204 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridin-2-ylmethyl)-piperazin-2-one

EXAMPLE 1205 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(5-methyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridin-2-ylmethyl)-piperazin-2-one

EXAMPLE 1206 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4,5,6,7-tetrahydro-thiazolo[4,5-c]pyridin-2-ylmethyl)-piperazin-2-one

EXAMPLE 1207 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(5-methyl-4,5,6,7-tetrahydro-thiazolo[4,5-c]pyridin-2-ylmethyl)-piperazin-2-one

EXAMPLE 1208 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4,7-dihydro-5H-thiazolo[4,5-c]pyridin-6-one

The following compounds are prepared according to the methods described above;

Example	Name	MS (m/z) (M+H)

1209	(R)-2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid amide	569
1210	(R)-4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-1-(4,5,6,7-tetrahydro-benzothiazol-2-ylmethyl)-piperazin-2-one	526
1211	(R)-2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid ethyl ester	544/546
1212	(R)-2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-4-methyl-thiazole-5-carboxylic acid dimethylamide	557
1213	(R)-4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-1-(4-pyridin-3-yl-thiazol-2-ylmethyl)-piperazin-2-one	549
1214	(R)-3-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-3-methyl-butyric acid ethyl ester	600
1215	(R)-2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid	516
1216	(R)-2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid dimethylamide	543
1217	(S)-2-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-(3S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid amide	513
1218	(S)-2-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-(3S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-thiazole-4-carboxylic acid ethyl ester	488
1219	(S)-2-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3(S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-thiazole-4-carboxylic acid dimethylamide	487
1220	(S)-(2-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3(S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-thiazol-4-yl)-acetic acid methyl ester	488
1221	(S)-4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3(S)-methoxymethyl-1-(4,5,6,7-tetrahydro-benzothiazol-2-ylmethyl)-piperazin-2-one	470

EXAMPLE 1222 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-hydroxy-4,5,6,7-tetrahydro-benzothiazol-2-ylmethyl)-piperazin-2-one

To a suspension of 2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-6,7-dihydro-5H-benzothiazol-4-one (7 mg, 0.01 mmol) in EtOH (1 mL) is added sodium borohydride (3 mg, 0.08 mmol). After 15 min the reaction is diluted with EtOAc and washed

with 1N HCl, $NaHCO_3$ and brine. The solution is dried (MgSO4) and concentrated to provide 4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-hydroxy-4,5,6,7-tetrahydro-benzothiazol-2-ylmethyl)-piperazin-2-one. ^1H NMR (300 MHz, $CDCl_3$) δ 7.88-7.82 (m, 3H), 7.46 (dd, 1H), 4.83-4.81 (m, 1H), 4.76 (s, 1H), 4.75 (s, 1H), 3.92 (s, 1H), 3.91 (s,1H), 3.62-3.55 (m, 2H), 3.47-3.41 (m, 2H), 2.76-2.62 (m, 2H), 2.05-1.78 (m, 4H); MS (Ion Spray) 498 $(M+H)^+$.

EXAMPLE 1223 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-6,7-dihydro-5H-benzothiazol-4-one oxime

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-6,7-dihydro-5H-benzothiazol-4-one (24 mg, 0.05 mmol), hydroxylamine hydrochloride (20 mg, 0.3mmol), sodium acetate (20 mg, 0.3 mmol) and EtOH (2 mL) are combined and stirred 3.5 h. The reaction is diluted with CH_2Cl_2 and washed with NH_4Cl, $NaHCO_3$ and concentrated to provide 2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-6,7-dihydro-5H-benzothiazol-4-one oxime. ^1H NMR (300 MHz, DMSO-d_6) δ 10.92 (s, 1H), 8.34 (d, 1H), 8.20 (s, 1H), 8.07 (d, 1H), 7.59 (dd, 1H), 4.70 (s, 2H), 3.87 (s, 2H), 3.49 (s, 4H), 2.74 (t, 2H), 2.61 (t, 2H), 1.81 (dt, 2H); MS (Ion Spray) 511 $(M+H)^+$.

EXAMPLE 1224a 1-(4-Amino-benzothiazol-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one and

EXAMPLE 1224b 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-5,6,7,8-tetrahydro-thiazolo[4,5-c]azepin-4-one

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-6,7-dihydro-5H-benzothiazol-4-one (60 mg, 0.12 mmol) is dissolved in $CHCl_3$ (4 mL) and sulfuric acid (0.5 mL) is added with vigorous stirring. Sodium azide (25 mg 0.4 mmol) is added and the reaction is stirred 1 ¾ h. The reaction is then added dropwise to a rapidly stirring mixture of $K_2CO_3/H_20/CH_2Cl_2$. The organic phase is separated and washed with water, dried ($MgSO_4$) and concentrated. The residue is purified by column chromatography (silica, 2% to 6% $MeOH/CH_2Cl_2$) to provide a mixture of two products.

The faster eluting product is the Semler-Wolff aromatization product, 1-(4-amino-benzothiazol-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one. ^1H NMR (300 MHz, DMSO-d_6) δ 8.32 (d, 1H), 8.21 (s, 1H), 8.07 (d, 1H), 7.59 (dd, 1H), 7.08 (t, 1H), 6.98 (d, 1H), 6.13 (d, 1H), 5.59 (s, 2H), 4.84 (s, 2H), 3.93 (s, 2H), 3.54 (s, 4H); MS (Ion Spray) 493 $(M+H)^+$.

The slower eluting product is the ring expanded lactam, 2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-5,6,7,8-tetrahydro-thiazolo[4,5-c]azepin-4-one. ^1H NMR (300 MHz, $CDCl_3$) δ 7.87-7.82 (m, 3H), 7.47 (dd, 1H), 6.47 (bs, 1H), 4.80 (m, 2H), 3.91 (s,2H),

3.65-3.61 (m, 2H), 3.46-3.42 (m, 2H), 3.37-3.32 (m, 2H), 3.07 (t, 2H) 2.17-2.10 (m, 2H); MS (Ion Spray) 511 $(M+H)^+$.

EXAMPLE 1225 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid dimethylamide

A: 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl-carboxylic acid

A solution of 2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl-carboxylic acid ethyl ester (75 mg, 0.15 mmol) is dissolved in THF/MeOH -3:1 (2 mL) and a solution of 1N NaOH is added (0.5 mL). The reaction is stirred for 2h and then diluted with EtOAc and washed with 2N HCl. The organic phase is dried (MgSO4) and concentrated to yield 2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl-carboxylic acid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.32 (d, 1H), 8.26 (s, 1H), 8.18 (s, 1H), 8.04 (d, 1H), 7.57 (dd, 1H), 4.74 (s, 2H), 3.87 (s, 2H), 3.49 (s, 4H); MS (Ion Spray) 471 $(M)^+$.

B: 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid dimethylamide

To a solution of 2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl-carboxylic acid (14 mg, 0.03 mmol) in N-methyl-pyrolidinone (0.3 mL) is added TBTU (0.05 mmol) and diisopropylethylamine (0.06 mmol) and dimethylamine hydrochloride (0.06). The reaction is stirred 3h and an additional aliquot of TBTU, DIEA and amine are added. The reaction is stirred 1h and the reaction is concentrated and purified by column chromatography (silica, 2% MeOH/EtOAc) to provide 2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid dimethylamide. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.77 (m, 4H), 7.47 (dd, 1H), 4.83 (s, 2H), 3.92 (s, 2H), 3.63-3.60 (m, 2H), 3.47-3.43 (m, 2H), 3.18 (s, 3H), 3.10 (s, 3H); MS (Ion Spray) 499 $(M+H)^+$.

When alternative amines are used in the above reaction the following products are isolated:

EXAMPLE 1226 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[4-(pyrrolidine-1-carbonyl)-thiazol-2-ylmethyl]-piperazin-2-one

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.87-7.81 (m, 3H), 7.47 (d, 1H), 4.81 (s, 2H), 3.92 (s, 2H), 3.82 (m, 2H), 3.72-3.61 (m, 4H), 3.46 (m, 2H), 1.97-1.87 (m, 4H); MS (ion spray) 525 $(M+H)^+$.

EXAMPLE 1227 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[4-(morpholine-4-carbonyl)-thiazol-2-ylmethyl]-piperazin-2-one

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88-7.82 (m, 4H), 7.46 (dd, 1H), 4.82 (s, 2H), 3.93 (s, 2H), 3.88-3.67 (m, 8H), 3.61 (m, 2H), 3.46 (m, 2H); MS (ion spray) 541 $(M+H)^+$.

EXAMPLE 1228 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[4-(piperazine-1-carbonyl)-thiazol-2-ylmethyl]-piperazin-2-one

As the TFA salt: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.9 (s (broad), 1H), 7.99 (s, 1H), 7.87-7.82 (m, 3H), 7.46 (dd, 1H), 4.80 (s, 2H), 4.39-3.96 (m (broad), 4H), 3.90 (s, 2H), 3.59 (m, 2H), 3.47 (m, 2H), 3.28 (s (broad), 4H); MS (ion spray) 540 $(M+H)^+$.

EXAMPLE 1229 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid N',N'-dimethyl-hydrazine

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.86-7.80 (m, 3H), 7.46-7.43 (m, 1H), 4.77 (s, 2H), 3.92 (s, 2H), 3.83 (m, 2H), 3.52 (m, 2H), 3.21 (s, 6H); MS (ion spray) 514 $(M+H)^+$.

EXAMPLE 1230 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid (2-hydroxy-ethyl)-methyl-amide

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91-7.81 (m, 4H), 7.46 (dd, 1H), 4.81 (s, 2H), 4.68 (t, 1H), 3.94 (s, 2H), 3.72 (m, 2H), 3.64-3.54 (m, 4H), 3.49 (m, 2H), 3.08 (s, 3H); MS (ion spray) 529 $(M+H)^+$.

EXAMPLE 1231 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[4-(3-hydroxy-pyrrolidine-1-carbonyl)-thiazol-2-ylmethyl]-piperazin-2-one

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, 1H), 7.87-7.82 (m, 3H), 7.45 (dd, 1H), 4.85 (s, 2H), 4.62-4.55 (m, 1H), 4.08-3.42 (m, 10H), 2.12-1.92 (m, 2H); MS (ion spray) 541 $(M+H)^+$.

EXAMPLE 1232 2-(4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid methoxy-methyl-amide

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.86-7.81 (m, 3H), 7.45 (dd, 1H), 4.85 (s, 2H), 3.92 (s, 2H), 3.72 (s, 3H), 3.62 (m, 2H), 3.45 (m, 2H), 3.39 (s, 3H); MS (ion spray) 515 $(M+H)^+$.

EXAMPLE 1233 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid isopropyl-methyl-amide

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87- 7.81 (m, 3H), 7.66 (m, 1H), 7.45 (dd, 1H), 4.95-4.89 (m, 0.5), 4.82 (s, 2H), 4.38-4.22 (m, 0.5), 3.91 (s, 2H), 3.68-3.59 (m, 2H), 3.48-3.42 (m, 2H), 2.92 (s (broad), 3H), 1.24-1.15 (m, 6H); MS (ion spray) 527 $(M+H)^+$.

EXAMPLE 1234 ({2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carbonyl}-methyl-amino)-acetic acid ethyl ester

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98-7.81 (m, 4H), 7.46 (dd,1H), 4.83 (s, 1H), 4.75 (s, 1H), 4.44 (s, 1H), 4.26-4.13 (m, 3H), 3.91 (s, 1H), 3.63-3.58 (m, 2H), 3.46-3.43 (m, 2H), 3.31 (s, 1.5), 3.15 (s, 1.5), 1.32-1.22 (m, 3H); MS (ion spray) 571 $(M+H)^+$.

EXAMPLE 1235 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxamide

MS (ion spray) 471 $(M+H)^+$.

EXAMPLE 1236 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid methylamide

MS (ion spray) 485 $(M+H)^+$.

EXAMPLE 1237 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid isopropylamide

MS (ion spray) 513 $(M+H)^+$.

When a {2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-acetic acid methyl ester is treated with NaOH under the conditions previously employed then the product obtained is:

EXAMPLE 1238 {2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-acetic acid.

^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD) δ 7.90-7.87 (m, 3H), 7.47 (dd, 1H), 7.17 (s, 1H), 4.80 (s, 2H), 3.93 (s, 2H), 3.75 (s, 2H), 3.60-3.58 (m, 2H), 3.50-3.48 (m, 2H); MS (Ion Spray) 486 $(M+H)^+$.

Amide bond formation using the conditions previously employed provides the following products using the amines shown

EXAMPLE 1239 2-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-acetamide

MS (ion spray) 485 $(M+H)^+$.

EXAMPLE 1240 2-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-N-methyl-acetamide

MS (ion spray) 499 $(M+H)^+$.

EXAMPLE 1241 2-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-N-isopropyl-acetamide

MS (ion spray) 527 $(M+H)^+$.

EXAMPLE 1242 2-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-N,N-dimethyl-acetamide

MS (ion spray) 513 $(M+H)^+$.

EXAMPLE 1243 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4,7-dihydro-5H-thiazolo[5,4-c]pyridin-6-one.

A: 5-Benzyloxycarbonylamino-3-oxo-pentanoic acid ethyl ester

Cbz-β-Alanine (5.0 g , 21.6 mmol) is dissolved in THF (10 mL). To this is added dropwise a solution of carbonyl diimidazole (3.5 g , 21.6 mmol) in THF (50 mL) and allowed to stir 16 hrs. This solution is then reduced to ~ 30 mL by rotary evaporation. In a separate flask (oven dried), isopropyl magnesium chloride in THF (2M) (16.2 mL, 32 mmol) is added and cooled to 0 °C and hydrogen ethyl malonate (4.28 g, 32.4 mmol) is added dropwise. The contents are allowed to stir at 0 °C for 30 min, allowed to warm to 25 °C and continue stirring for another 30 min, and finally warmed to 40 °C for 30 min. The contents are then cooled to 0 °C and the contents of the first flask are added dropwise. The reaction is allowed to gradually come to 25 °C and continue stirring for 4 hrs. The reaction is poured into 100 mL of ice cold 1 N H_3PO_4 and allowed to stir for 30 min. The contents are extracted (3 x 100 mL) with ethyl acetate. The combined organic layers are then washed (3 x 100 mL) with saturated sodium bicarbonate followed by (3 x 100 mL) with brine. The organic layer is dried over $MgSO_4$, filtered and reduced to an oil by rotary evaporation to provide 5-benzyloxycarbonylamino-3-oxo-pentanoic

acid ethyl ester. The product is used as is without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (s, 5H), 5.25 (bm, 1H), 5.06 (s, 2H), 4.17 (q, 2H), 3.42 (m, 5H), 2.78 (t, 2H), 1.25 (t, 3H); MS (ion spray) 294 $(M+H)^+$.

B: 5-Benzyloxycarbonylamino-4-bromo-3-oxo-pentanoic acid ethyl ester

5-Benzyloxycarbonylamino-3-oxo-pentanoic acid ethyl ester (1.0 g, 3.4 mmol) is dissolved in glacial acetic acid (10mL) and pyridinium bromide perbromide (1.1 g, 3.4 mmol) of is added. The reaction stirred 16 hrs and then poured into H_2O (100 mL) and extracted with ethyl acetate (2 x 100 mL). The organic layers are combined and washed with H_2O (2 x 100 mL) and with brine (2 x 100 mL). The organic layer is dried over MgSO4, filtered and reduced to an oil by rotary evaporation. The crude product is purified by flash chrom-atography on silica gel using 25% ethyl acetate / hexane as the eluent to provide 5-benzyloxycarbonylamino-4-bromo-3-oxo-pentanoic acid ethyl ester. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (s, 5H), 5.27 (m, 1H), 5.09 (s, 2H), 4.67 (t, 1H), 4.17 (q, 2H), 3.72 (m, 4H), 1.27 (t, 3H); MS (ion spray) 372 $(M+H)^+$.

C: {5-(Benzyloxycarbonylamino-methyl)-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-acetic acid ethyl ester

A suspension of 2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-1-yl]-thioacetamide (200 mg, 0.5 mmol) and 5-benzyloxycarbonylamino-4-bromo-3-oxo-pentanoic acid ethyl ester (370 mg, 1.0 mmol) is heated at 90 °C in a mixture of toluene/t-butanol, 1:1 (5 mL) for 16 h. The reaction is concentrated and purified using column chromatography (silica, 2%MeOH/CH_2Cl_2) to provide {5-(benzyloxycarbonylamino-methyl)-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-acetic acid ethyl ester. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.81 (m, 3H), 7.45 (dd, 1H), 7.32 (s, 5H), 7.45 (bt, 1H), 5.07 (s, 2H), 4.73 (s, 2H), 4.42 (d, 2H), 4.13 (q, 2H), 3.90 (s, 2H), 3.76 (s, 2H), 3.61-3.55 (m, 2H), 3.50-3.43 (m, 2H), 1.24 (t, 3H); MS (ion spray) 677 $(M+H)^+$.

D: {5-Aminomethyl-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-acetic acid ethyl ester

{5-(Benzyloxycarbonylamino-methyl)-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-acetic acid ethyl ester (40 mg, 0.06 mmol) is treated with 30% HBr/HOAc (1 mL) for 7 h. Ether (10 mL) is added and the resulting precipitate is washed twice with ether. The resulting salt is partitioned between EtOAc (15 mL) and $NaHCO_3$ solution (10 mL). The organic phase is washed with NaHCO3 and brine (2 x 10 mL), dried ($MgSO_4$) and concentrated to provide {5-aminomethyl-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-

piperazin-1-ylmethyl]-thiazol-4-yl}-acetic acid ethyl ester. ^{1}H NMR (300 MHz, DMSO) δ 8.32 (d, 1H), 8.17 (s, 1H), 8.08-8.02 (m, 2H), 7.57 (dd, 1H), 4.62 (s, 2H), 4.02 (q, 2H), 3.81 (s, 2H), 3.74 (s, 2H), 3.64 (s, 2H), 3.48-3.35 (m, 4H), 2.48 (t, 3H); MS (ion spray) 543 $(M+H)^+$.

E: 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4,7-dihydro-5H-thiazolo[5,4-c]pyridin-6-one

{5-Aminomethyl-2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-acetic acid ethyl ester (12 mg, 0.02 mmol) is heated in EtOH (3 mL) for 3 days at 70 °C. The precipitate which is formed is filtered to provide 2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4,7-dihydro-5H-thiazolo[5,4-c]pyridin-6-one. ^{1}H NMR (300 MHz, DMSO) δ 8.31 (d, 1H), 8.08-8.02 (m, 2H), 7.55 (dd, 1H), 4.67 (s, 2H), 4.36 (s (broad), 2H), 3.84 (s, 2H), 3.60-3.54 (m, 4H), 3.38 (t, 2H); MS (LC/MS-ESI) 496 $(M+H)^+$.

EXAMPLE 1244 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-piperidin-4-ylmethyl-piperazin-2-one.

A: 4-Hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester

Isonipecotic acid (19.6g, 76 mmol) is dissolved in THF (200 mL) and cooled to 0 °C and lithium aluminum hydride is added portionwise over 10 minutes. The reaction is allowed to stir at 25 °C for 16 h. The reaction is then cooled to 0 °C and water (6 mL) is added dropwise followed by 15% NaOH (6 mL). After 20 minutes, water (18 mL) is added and the reaction is stirred 30 min. The reaction is filtered, and the filtrate is concentrated and recrystallized from hexane to provide 4-hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester. mp 67-75 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.11 (bd, 2H), 3.50 (d, 2H), 2.70 (dd, 2H), 1.73-1.60 (m, 3H), 1.45 (s, 9H), 1.14 (ddd, 2H); MS (ion spray) 216 $(M+H)^+$.

B: 4-Bromomethyl-piperidine-1-carboxylic acid tert-butyl ester

A solution of 4-hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester (2.30 g, 10.7 mmol) and carbon tetrabromide (4.43 g, 13.4 mmol) in CH_2Cl_2 (40 mL) is cooled to 0 °C. Triphenylphosphine (4.21g, 16.0 mmol) is added and the reaction is stirred at 25 °C for 1h. The reaction is concentrated and ether is added to the residue. The mixture is filtered and washed with ether. The filtrate is concentrated and purified by column chromatography (silica, 20% EtOAc/hexane) to provide 4-bromomethyl-piperidine-1-carboxylic acid tert-butyl ester as a crystaline solid upon standing. Mp 48-50 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.13 (bm, 2H), 3.29 (d, 2H), 2.70 (dd, 2H), 1.85-1.73 (m, 3H), 1.46 (s, 9H), 1.28-1.13 (m, 2H); MS (EI) 277 (M)+.

C: 4-(1-tert-Butoxycarbonyl-piperidin-4-ylmethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester

Sodium hydride (60%, 0.27 g, 6.7 mmol) is added to a solution of 4-benzyloxycarbonyl-2-oxo-piperazine (1.58 g, 6.7 mmol) in dry DMF (40 mL). After 30 minutes 4-bromomethyl-piperidine-1-carboxylic acid tert-butyl ester (1.87g, 6.7 mmol) is added and the reaction is allowed to stir for 16h. The solvent is removed in vacuo and the residue is dissolved in ether and washed with NH_4Cl. The aqueous phase is back-extracted with ether and the combined ether fractions are washed with water and brine to provide 4-(1-tert-butoxycarbonyl-piperidin-4-ylmethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester which is used without futher purification. ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (s, 5H), 5.16 (d, 2H), 4.16 (s, 2H), 4.13 (br, 2H), 3.73-3.69 (m, 2H), 3.44-3.30 (m, 6H), 2.68 (bt, 2H), 1.85-1.73 (m, 1H), 1.58 (bd, 2H), 1.46 (s, 9H), 1.25-1.10 (m, 2H); MS (ion spray) 432 (M+H)+.

D: 4-(2-Oxo-piperazin-1-ylmethyl)-piperidine-1-carboxylic acid tert-butyl ester

A solution of 4-(1-tert-butoxycarbonyl-piperidin-4-ylmethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester (2.3 g, 5.4 mmol) in methanol (75 mL) is purged with nitrogen and 10% Pd on carbon (0.3 g) is added, and the reaction is again purged with nitrogen. The reaction is placed on a Parr shaker under hydrogen for 16h. After the system is purged of hydrogen, the catalyst is filtered and washed with methanol. The filtrate is concentrated to provide 4-(2-oxo-piperazin-1-ylmethyl)-piperidine-1-carboxylic acid tert-butyl ester which is used without further purification. MS (EI) 298 (M+H)+.

E: 4-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-piperidine-1-carboxylic acid tert-butyl ester

To a solution of 4-(2-oxo-piperazin-1-ylmethyl)-piperidine-1-carboxylic acid tert-butyl ester (1.44 g, 4.8 mmol) in CH_2Cl_2 (75 mL) and MeCN (10 mL) is added diisopropylethylamine (1.3 mL, 4.8 mmol) followed by 6-chloro-benzo[b]thiophene-2-sulfonyl chloride (1.29 g, 4.8 mmol), and the reaction is allowed to stir 16 h. The reaction is diluted with CH_2Cl_2 and washed with 1N HCl and NaHCO3, dried and concentrated. The residue is purified by column chromatography (silica, 40% EtOAc/ CH_2Cl_2) to provide 4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-piperidine-1-carboxylic acid tert-butyl ester. ^1H NMR (300 MHz, $CDCl_3$) δ 7.88-7.83 (m, 3H), 7.47 (dd, 1H), 4.1 (br, 2H), 3.86 (s, 2H), 3.46 (bs, 4H), 3.25 (br, 2H), 2.61 (t, 2H), 1.87-1.75 (m, 1H), 1.51 (d, 2H), 1.41 (s, 9H), 1.10 (ddd, 2H); MS (Ion spray) 528 $(M+H)^+$.

F: 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-piperidin-4-ylmethyl-piperazin-2-one

Trifluoroacetic acid (4 mL) is added to a solution of 4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-piperidine-1-carboxylic acid tert-butyl ester (1.1 g, 2.0 mmol) in CH_2Cl_2 (15 mL). After 1 h the reaction is concentrated and the residue is dissolved in CH_2Cl_2 and washed with Na_2CO_3, dried ($MgSO_4$) and concentrated to provide 4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-1-piperidin-4-ylmethyl-piperazin-2-one. ^1H NMR (300 MHz, $CDCl_3$) δ 7.87-7.83 (m, 3H), 7.46 (dd, 1H), 3.86 (dd, 2H), 3.45 (s, 2H), 3.23 (d, 2H), 3.07 (d, 2H), 2.54 (dt, 2H), 2.39 (s, 1H), 1.83-1.75 (m, 1H), 1.56 (d, 2H), 1.24-1.11 (m, 2H); MS (Ion spray) 428 $(M+H)^+$.

EXAMPLE 1245 4-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-piperidine-1-carboxylic acid amide

To a solution of 4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-1-piperidin-4-ylmethyl-piperazin-2-one (20 mg, 0.047 mmol) in a mixture of 1,2-dichloroethane (1 mL) and THF (1 mL) is added trimethylsilyl isocyanate (0.006 mL, 0.05 mmol) and stirred 60 hours. The reaction is concentrated and purified by column chromatography (silica, 20% methanol/dichloromethane) to provide 4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-piperidine-1-carboxylic acid amide. ^1H NMR (300 MHz, CD_3OD) d 8.09 (s, 1H), 8.02 (d, 2H), 7.53 (dd, 1H), 3.90 (d, 4H), 3.49 (d, 4H), 3.30-3.24 (m, 2H), 2.65 (dt, 2H), 1.49 (d, 2H), 1.12-0.97 (m, 2H); MS (Ion spray) 471 (M+H).

EXAMPLE 1246 2-{4-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-piperidin-1-yl}-acetamide

To a solution of 4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-1-piperidin-4-ylmethyl-piperazin-2-one (20 mg, 0.047 mmol) in N-methylpyrrolidinone (0.5 mL) is added 2-chloroacetamide (9 mg, 0.094 mmole) and diisopropylethylamine (0.016 mL, 0.094 mmole) and heated at 120 °C for 16 h. The reaction is concentrated and purified by column chromatography (silica, 5% methanol/dichloromethane) to provide 2-{4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-piperidin-1-yl}-acetamide. ^1H NMR (300 MHz, $CDCl_3$) d 7.88-7.83 (m, 3H), 7.47 (dd, 1H), 6.98 (bs, 1H), 5.30 (bs, 1H), 3.86 (s, 2H), 3.46 (s, 4H), 3.28 (d, 2H), 2.95 (s, 2H), 2.82 (d, 2H), 2.06 (t, 2H), 1.69-1.50 (m, 3H), 1.33-1.25 (m, 2H); MS (Ion spray) 485 $(M+H)^+$.

EXAMPLE 1247 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[1-(2-chloro-pyrimidin-4-yl)-piperidin-4-ylmethyl]-piperazin-2-one

To a solution of 4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-1-piperidin-4-ylmethyl-piperazin-2-one (40 mg, 0.094 mmole) in n-butanol (1.0 mL) is added 2,4-dichloropyrimidine (14, 0.094 mmole) and diisopropylethylamine (0.016 mL, 0.094 mmole) and this mixture is heated at 110°C for 4 hours. The reaction is concentrated and purified by column chromatography (silica, 25% ethyl acetate/dichloromethane) to yield 4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-1-[1-(2-chloro-pyrimidin-4-yl)-piperidin-4-ylmethyl]-piperazin-2-one. ^{1}H NMR (300 MHz, $CDCl_3$) d 8.01 (d, 1H), 7.89-7.87 (m, 3H), 7.48 (dd, 1H), 6.35 (d, 1H), 4.41-4.20 (m, 2H), 3.87 (s, 2H), 3.48 (s, 4H), 3.28 (dd, 2H), 2.05-1.95 (m, 1H), 1.67 (d, 2H), 1.31-1.20 (m, 2H); MS (Ion spray) 542 $(M+H)^+$.

EXAMPLE 1248 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-piperazin-2-one

To a solution of 4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-1-[1-(2-chloro-pyrimidin-4-yl)-piperidin-4-ylmethyl]-piperazin-2-one (17 mg, 0.031 mmole) in ethanol (1 mL) is added a 40% solution of dimethylamine (11 mg, 0.094 mmole). This mixture is heated at 80 °C in a sealed tube 16h. The reaction is concentrated and lyophilized to provide 4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-piperazin-2-one. ^{1}H NMR (300 MHz, $CDCl_3$) d 7.93-7.84 (m, 4H), 7.48 (dd, 1H), 5.84 (d, 1H), 4.32 (d, 2H), 3.87 (s, 2H), 3.47 (s, 4H), 3.26 (d, 2H), 3.14 (s, 6H), 1.99-1.90 (m, 1H), 1.62 (d, 2H), 1.27-1.17 (m, 2H); MS (Ion spray) 549 $(M+H)^+$.

Using the procedures the following compounds can be prepared;

Example	Name
1249	(R)-4-(5-chloro-1H-indole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-piperazin-2-one
1250	(R)-4-(6-chloro-1H-indole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-piperazin-2-one
1251	(R)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-piperazin-2-one
1252	(R)-4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-methyl-piperazin-2-one
1253	(R)-4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-methoxymethyl-piperazin-2-one
1254	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[1-(2-dimethylamino-

	pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-oxo-piperazine-2-carboxylic acid methyl ester
1255	(R)-4-(5-chloro-1H-indole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-methyl-piperazin-2-one
1256	(R)-4-(5-chloro-1H-indole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-methoxymethyl-piperazin-2-one
1257	4-(5-chloro-1H-indole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-oxo-piperazine-2-carboxylic acid methyl ester
1258	(R)-4-(6-chloro-1H-indole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-methyl-piperazin-2-one
1259	(R)-4-(6-chloro-1H-indole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-methoxymethyl-piperazin-2-one
1260	4-(6-chloro-1H-indole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-oxo-piperazine-2-carboxylic acid methyl ester
1261	(R)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-methyl-piperazin-2-one
1262	(R)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-methoxymethyl-piperazin-2-one
1263	4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-oxo-piperazine-2-carboxylic acid methyl ester

EXAMPLE 1264 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-{1-[2-(2-hydroxy-ethylamino)-pyrimidin-4-yl]-piperidin-4-ylmethyl}-piperazin-2-one.

To a solution of 4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-1-[1-(2-chloro-pyrimidin-4-yl)-piperidin-4-ylmethyl]-piperazin-2-one (0.40 g, 0.74mmol) in EtOH is added ethanolamine (0.089 mL, 1.5 mmol). The solution is heated to reflux for 18 h and evaporated to dryness. The residue is chromatographed eluting successively with 1%, 2% and 4% MeOH in CH_2Cl_2. Fractions containing only product are combined and the solvent evaporated. Trituration with ether afforded the title compound as a yellow solid: MS (ESI): *m/z* 565 (M^+ + H).

By substituting ethanolamine with the corresponding amine, the following products can similarly be prepared:

Example 1265

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-{1-[2-(4-dimethylamino-butylamino)-pyrimidin-4-yl]-piperidin-4-ylmethyl}-piperazin-2-one

Example 1266

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-{1-[2-(3-imidazol-1-yl-propylamino)-pyrimidin-4-yl]-piperidin-4-ylmethyl}-piperazin-2-one

Example 1267

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-{1-[2-(3-morpholin-4-yl-propylamino)-pyrimidin-4-yl]-piperidin-4-ylmethyl}-piperazin-2-one

Example 1268

4-[(4-{4-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-piperidin-1-yl}-pyrimidin-2-yl)-methyl-amino]-butyric acid

Example 1269

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-{1-[2-(2-dimethylamino-ethoxy)-pyrimidin-4-yl]-piperidin-4-ylmethyl}-piperazin-2-one

Example 1270

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1-{2-[2-(2-oxo-imidazolidin-1-yl)-ethylamino]-pyrimidin-4-yl}-piperidin-4-ylmethyl)-piperazin-2-one

Example 1271

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-{1-[2-(2-dimethylamino-ethylsulfanyl)-pyrimidin-4-yl]-piperidin-4-ylmethyl}-piperazin-2-one

EXAMPLE 1272 4-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid

To a solution of 4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-1-piperidin-4-ylmethyl-piperazin-2-one (20 mg, 0.047 mmol) in n-butanol (0.5 mL) is added 6-chloronicotinamide (15 mg, 0.094 mmole) and diisopropylethylamine (0.016 mL, 0.094 mmole) and heated at 110 °C 16 h. The reaction is concentrated and purified by column chromatography (silica, 20% methanol/dichloromethane) to provide 4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid. ^{1}H NMR (300

MHz, CD_3OD) δ 8.59 (d, 1H), 8.11-7.92 (m, 3H), 7.54 (dd,1H), 6.72 (d, 1H), 4.27 (d, 1H), 3.92 (s, 2H), 3.57-3.47 (m, 4H), 3.25 (d, 2H), 2.79-2.71 (dt, 2H), 1.96-1.80 (m, 1H), 1.50 (d, 2H), 1.29-1.06 (m, 2H); MS (Ion spray) 549 $(M+H)^+$.

Using the corresponding halide the following compounds can be similarly prepared:

EXAMPLE 1273 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1-pyrimidin-2-yl-piperidin-4-ylmethyl)-piperazin-2-one

^1H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, 2H), 7.88-7.83 (m, 3H), 7.48 (d, 1H), 6.44 (t, 1H), 4.71 (d, 2H), 3.87 (s, 2H), 3.47 (s, 4H), 3.26 (d, 2H), 2.76 (dt, 2H), 2.00-1.91 (m, 1H), 1.62 (d, 2H), 1.26-1.21 (m, 2H) ; MS (Ion spray) 506 $(M+H)^+$.

EXAMPLE 1274 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1-pyrazin-2-yl-piperidin-4-ylmethyl)-piperazin-2-one

^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, 2H), 7.89-7.84 (m, 4H), 7.48 (dd, 1H), 4.27 (d, 2H), 3.88 (s, 2H), 3.48 (s, 2H), 3.28 (d, 2H), 2.80 (t, 2H), 2.01-1.90 (m, 1H), 1.65 (d, 2H), 1.32 (m, 2H); MS (Ion spray) 506 $(M+H)^+$.

EXAMPLE 1275 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-ylmethyl)-piperazin-2-one

^1H NMR (300 MHz, $CDCl_3$) δ 8.15 (t, 1H), 7.89-7.84 (m, 3H), 7.49-7.41 (m, 2H), 6.63-6.56 (m, 2H), 4.23 (d, 2H), 3.88 (s, 2H), 3.48 (s, 4H), 3.27 (d, 2H), 2.73 (dt, 2H), 1.93-1.86 (m, 1H), 1.60 (t, 2H), 1.32-1.19 (m, 2H); MS (Ion spray) 505 $(M+H)^+$.

EXAMPLE 1276 4-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-carboxylic acid

^1H NMR (300 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.39-8.29 (m, 2H), 7.99-7.84 (m, 3H), 7.49-7.45 (m, 1H), 7.08 (q, 1H), 5.65 (s, 1H), 3.87 (d, 2H), 3.48 (d, 6H), 2.81 (t, 1H), 2.57 (dt, 1H), 1.85-1.76 (m, 1H), 1.73-1.69 (m, 2H), 1.43-1.37 (m, 2H); MS (Ion spray) 548 $(M+H)^+$.

EXAMPLE 1277 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(6'-methoxy-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-ylmethyl)-piperazin-2-one

^1H NMR (300 MHz, $CDCl_3$) δ 7.88-7.84 (m, 3H), 7.47 (dd, 1H), 7.37 (t, 1H), 6.12 (dd, 1H), 6.03 (dd, 1H), 4.24 (d, 2H), 3.88 (s, 2H), 3.84 (s, 3H), 3.48 (s, 4H), 3.27 (d, 2H), 2.71 (dt, 2H), 1.95-1.84 (m, 1H), 1.61 (d, 2H), 1.32-1.22 (m, 2H); MS (Ion spray) 535 $(M+H)^+$.

Preparation of the intermediate,
4-Bromomethyl-6'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl.

A: 6'-Methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-carboxylic acid ethyl ester
In a round-bottom flask, 20 ml of anhydrous toluene is added and degassed several times from vacuum/N_2. 2-methoxy-5-bromopyridine (752 mg, 4.0 mmol), ethyl isonipecotate (740 mg, 4.8 mmol), sodium t-butoxide (537 mg, 5.6 mmol), $Pd_2(DBA)_3$ (73 mg, 2 mol%) and of BINAP (100 mg, 0.16 mmol) are added and heated to 70 °C under N_2 for 16 hrs. The reaction is cooled to r.t. and taken up in 100 ml of ethyl ether and washed with brine (2 x 50 ml). The ether is dried over $MgSO_4$, filtered and reduced to an oil under vacuum. The compound is purified by flash chromatography on silica gel using 20 % ethyl acetate / hexane as the eluent to provide 6'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-carboxylic acid ethyl ester. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, 1H), 7.28 (dd, 1H), 6.66 (d, 1H), 4.15 (q, 2H), 3.87 (s, 3H), 3.42 (dt, 2H), 2.71 (dt, 2H), 2.39 (m, 1H), 2.03 (m, 2H), 1.90 (m, 2H), 1.26 (t, 3H); MS (EI) 264 $(M)^+$.

B: (6'-Methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-methanol
A round bottom flask is charged with anhydrous THF (8 mL) and LAH (122 mg, 3.17 mmol) is added. The contents are placed under N_2 and cooled to 0 °C. To this is added a solution of 6'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-carboxylic acid ethyl ester (400 mg, 1.51 mmol) in THF (2 ml) over 5 min. The reaction is allowed to come to r.t. and continue to stir for an additional hour. 4 drops of H_2O are added, followed by 4 drops of 15% $NaOH_{(aq)}$ and allowed to stir at r.t. for 20 min. 0.5 mL of H_2O are added, and the contents are filtered through a pad of celite and washed with THF. The solution is reduced to an oil under vacuum, and purified by flash chromatography on silica gel using 3% methanol / methylene chloride as the eluent to provide (6'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-methanol. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, 1H), 7.29 (dd, 1H), 6.66 (d, 1H), 3.88 (s, 3H), 3.53 (m, 4H), 2.65 (dt, 2H), 1.85 (m, 2H), 1.65 (m, 1H), 1.42 (m, 2H); MS (EI) 222 $(M)^+$.

C: 4-Bromomethyl-6'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl
(6'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-yl)-methanol (300 mg, 1.35 mmol) is dissolved in methylene chloride (10 mL). carbon tetrabromide (561 mg, 1.69 mmol) is added and dissolved. The solution is cooled to 0 °C and triphenylphoshine (529 mg, 2.02 mmol) is added portionwise. The reaction is allowed to come to r.t. and is stirred for 30 min. The volume is then reduced under vacuum to ~ 2 ml and purified by flash chromatography on silica gel

using 2% methanol / methylene chloride as the eluent to provide 4-bromomethyl-6'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl. ^{1}H NMR (300 MHz, CD_3OD) δ 7.74 (d, 1H), 7.43 (dd, 1H), 6.72 (d, 1H), 3.83 (s, 3H), 3.54 (m, 2H), 3.38 (d, 2H), 2.65 (dt, 2H), 1.94 (m, 2H), 1.75 (m, 1H), 1.44 (m, 2H); MS (EI) 284 $(M)^+$.

The above alkylating reagent, 4-bromomethyl-6'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl, can be used to provide:

EXAMPLE 1278 4-(6-Chloro-benzo[b]thiophene-sulfonyl)-1-(6'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-ylmethyl)-piperazin-2-one
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.81 (m, 3H), 7.50-7.43 (m, 2H), 6.88 (dd, 1H), (d, 1H), 3.85 (s, 5H), 3.48-3.15 (m, 7H), 3.29-3.17 (m, 2H), 2.89-2.81 (m, 1H), 2.25-2.12 (m, 1H), 1.65-1.56 (m, 4H); MS (ion spray) 535 $(M+H)^+$.

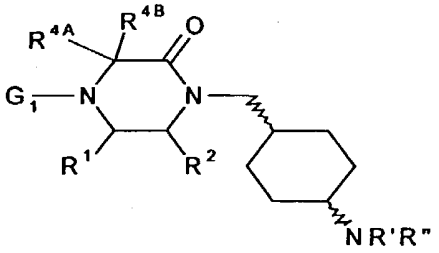
EXAMPLE 1279 O-Phenyl-1-cyano-3-{4-[(chlorobenzo[b]thiophene-2-sulfonyl)-2-(keto)piperazin-1-yl]methylpiperdinyl} isourea
To a suspension of 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-piperidin-4-ylmethyl-piperazin-2-one (0.90 g, 2.1 mmol) in 2-propanol (20 mL) is added diphenyl cyanocarbonimidate (0.50 g, 2.1 mmol). After stirring for 18 h, TLC (4% MeOH in CH_2Cl_2) indicated a mixture of starting material and primarily one faster migrating product. Additional diphenyl cyanocarbonimidate (0.50 g) is added and the reaction mixture is heated to 80 °C for 2 h. Upon cooling to rt the precipitate which formed is collected, washed with 2-propanol and air-dried to afford the title compound as an off- white solid; yield 0.48g. A sample is further purified by chromatography eluting successively with 1%, 2% and 4% MeOH in CH_2Cl_2 to afford a chromatographically pure white solid: MS (ESI): *m/z* 572 $(M^+ + H)$.

EXAMPLE 1280 Preparation of N,N Dimethyl-2-{4-[6-(chlorobenzo[b]thiophene-2-sulfonyl)-2-(keto)piperazin-1-yl]methylpiperdin-1-yl]} cyanoformamidine.
To a solution of O-phenyl-1-cyano-3-{4-[(chlorobenzo[b]thiophene-2-sulfonyl)-2-(keto)piperazin-1-yl]methylpiperdinyl} isourea (0.10 g, 0.18 mmol) in MeOH (10 mL) is added 40% aqueous dimethylamine (10 mL) and the reaction is stirred at rt for 72 h. The solvents are evaporated and the residue is chromatographed eluting successively with 1% and 2% MeOH in CH_2Cl_2. Fractions containing only product are concentrated and the residue is triturated with ether to afford the title compound as a white solid; yield 17 mg: MS (ESI): *m/z* 523 $(M^+ + H)$.

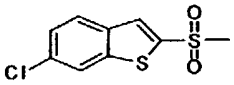
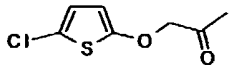
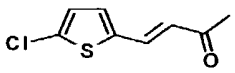
EXAMPLE 1281 Preparation of N-Methyl-2-{4-[6-(chlorobenzo[b]thiophene-2-sulfonyl)-2-(keto)piperazin-1-yl]methylpiperdin-1-yl]} cyanoformamidine.

The title compound is prepared as a white solid using the procedure of Example 3 except substituting methylamine for dimethylamine: MS (ESI): *m/z* 509 (M^+ + H).

Other, 4-(methylpiperin-1-yl) cyanoformamidine compounds can be prepared from intermediates having the structure of formula including but not limited to:



wherein G-1 includes but is not limited to


, 
, 
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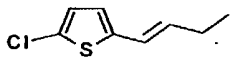
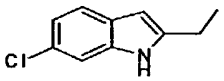

, and 
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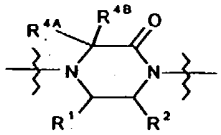
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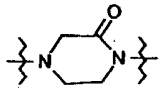
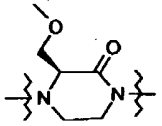
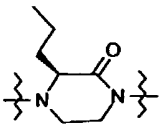
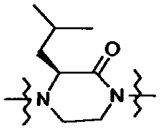
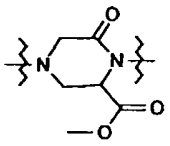
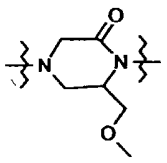

, 
, 


, 
, and 
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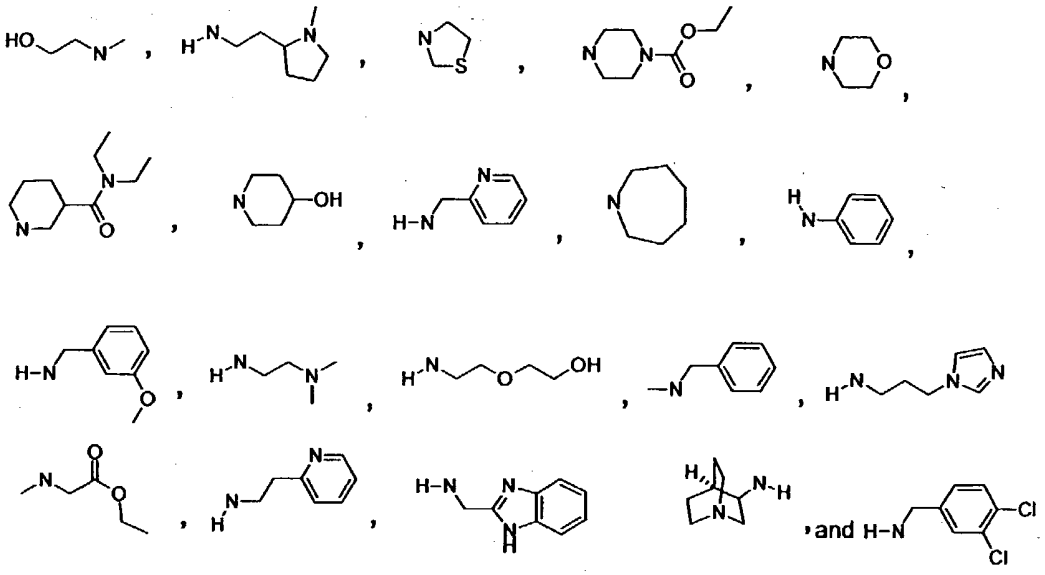


Example 1282 Preparation of N-trans-[{4-(5-Chloro-thiophen-2-yloxy)-acetyl-2-keto-3-(*S*)-methoxymethyl}-piperazin-1-yl]methylcyclohexyl-cyanoguanidine

a. Dimethoxymethyl-(2,3-dioxa-spiro[4.5]dec-8-ylmethyl)-amine

8-Carboxaldehyde-1,4-dioxa-spiro[4.5]decane (4.4 g, 26 mmol), prepared according to the method of Pearson et al. (*J. Org. Chem.* 62, 1997, 5284), aminoacetaldehyde dimethyl acetal (3.3 g, 0.31 mmol), acetic acid (1.6 g, 0.26 mmol) and sodium cyanoborohydride (2.0 g, 0.31 mmol) are stirred in methanol (140 mL) for 6 h. The methanol is evaporated and the residue is partitioned between ethyl acetate (200 mL) and 1 N NaOH (100 mL). The organic phase is dried (Na_2SO_4) and is evaporated to provide the intermediate title compound as a yellow oil (7.2 g) which is used without further purification. MS (EI), 259 $[M]^+$.

b. {1-[2,2-Dimethoxy-ethyl)-(2,3-dioxa-spiro[4.5]dec-8-ylmethyl)-carbamoyl]-2-(*S*)-methoxyethyl}-carbamic acid benzyl ester

Dimethoxymethyl-(2,3-dioxa-spiro[4.5]dec-8-ylmethyl)-amine (6.6 g, 26 mmol), (*S*)-(2-benzyloxycarbonylamino-3-methoxy)-propionic acid (7.2 g, 28 mmol), [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (12 g, 31 mmol) and N,N-diisopropylethylamine (7.7 g, 60 mmol) are stirred in DMF (200 mL) for 18 h. The DMF is evaporated and the residue diluted with ethyl acetate (200 mL). The organic phase is washed with water (50 mL), 2 N HCl (50 mL), 1 N NaOH (50 mL), is dried ($MgSO_4$) and is evaporated to

provide the intermediate title compound as a yellow oil (13 g) which is used without further purification. MS (ES), 495 $[M+H]^+$.

c. 4-(1,4-Dioxa-spiro[4.5]dec-8-ylmethyl)-2-(*S*)-methoxymethyl-3-oxo-3,4-dihydro-2H-pyrazine-1-carboxylic acid benzyl ester

{1-[2,2-Dimethoxy-ethyl)-(2,3-dioxa-spiro[4.5]dec-8-ylmethyl)-carbamoyl]-2-(*S*)-methoxyethyl}-carbamic acid benzyl ester (12.8 g, 26 mmole) and *p*-toluenesulphonic acid monohydrate (0.74 g, 3.9 mmol) are placed in toluene (150 mL) and stirred at 60-70°C for 7 h. The mixture is evaporated and the residue is purified by flash chromatography (silica gel, 2:1 hexanes/ethyl acetate) to provide the intermediate title compound as a clear colorless oil (5.0 g, 45%). MS (ES), 431 $[M+H]^+$.

d. 1-(1,4-Dioxa-spiro[4.5]dec-8-ylmethyl)-2-(*S*)-methoxymethyl-piperazin-2-one

4-(1,4-Dioxa-spiro[4.5]dec-8-ylmethyl)-2-(*S*)-methoxymethyl-3-oxo-3,4-dihydro-2H-pyrazine-1-carboxylic acid benzyl ester (4.7 g, 11 mmol) and 10% Pd on carbon (1.0 g) are stirred in methanol (150 mL) under a hydrogen atmosphere for 18 h. The mixture is filtered through Celite® and is evaporated to provide the intermediate title compound as a clear colorless oil (3.3 g, 11 mmol). MS (EI), 298 $[M]^+$.

e. 4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-(1,4-dioxa-spiro[4.5]dec-8-ylmethyl)-3-(*S*)-methoxymethyl-piperazin-2-one

1-(1,4-Dioxa-spiro[4.5]dec-8-ylmethyl)-2-(*S*)-methoxymethyl-piperazin-2-one (3.3 g, 11 mmol), (5-chloro-thiophen-2-yloxy)-acetic acid (2.1 g, 11 mmol), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (3.9 g, 12 mmol) and triethylamine (3.3 g, 33 mmol) are stirred in DMF (100 mL) for 8 h. The mixture is evaporated and is diluted with ethyl acetate (200 mL). The organic phase is washed with water, 2 N HCl, 1 N NaOH and brine, is dried ($MgSO_4$) and is evaporated. The residue is purified by flash chromatography (silica gel, 4:1 ethyl acetate/hexanes) to provide the intermediate title compound as a clear colorless oil (2.8g, 54%). MS (ES), 473 $[M+H]^+$.

f. 4-[(5-Chlorothiophen-2-yloxy)-acetyl]-3-(*S*)-methoxymethyl-1-(4-oxocyclohexylmethyl)-piperazin-2-one

4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-(1,4-dioxa-spiro[4.5]dec-8-ylmethyl)-3-(*S*)-methoxymethyl-piperazin-2-one (2.8 g, 5.9 mmol) is placed in 80:20 acetic acid/water and heated at 65°C for 0.2 h. The mixture is evaporated and is diluted with ethyl acetate (200 mL). The organic phase is washed with 1 N NaOH, is dried ($MgSO_4$) and is evaporated to provide the intermediate title compound as a clear colorless oil (2.4 g, 95%). MS (ES), 429 $[M+H]^+$.

g. 1-cis-[4-(Amino)-cyclohexylmethyl]-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(*S*)-methoxymethyl-piperazin-2-one and 1-trans-[4-(amino)-cyclohexylmethyl]-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(*S*)-methoxymethyl-piperazin-2-one

Sodium cyanoborohydride (0.075 g, 1.2 mmol) is added to a mixture of 4-[(5-Chlorothiophen-2-yloxy)-acetyl]-3-(*S*)-methoxymethyl-1-(4-oxocyclohexylmethyl)-piperazin-2-one (0.5 g, 1.2 mmol) and ammonium acetate (0.9 g, 12 mmol) in anhydrous methanol (20 mL). The mixture is stirred 18 h and is concentrated *in vacuo*. The residue is diluted with EtOAc (20 mL) and is washed with 1N NaOH. The organic phase is dried (Na_2SO_4) and is evaporated to provide the intermediate title compound as a mixture of cis and trans isomers (0.49 g, 98%) which is used without further purification. MS (ES), 430 $[M+H]^+$.

h. N-trans-({[4-(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(*S*)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-cyclohexyl)-N'-cyano-O-phenylisourea

N-(cis/trans)-({[4-(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(*S*)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-cyclohexyl)-N'-cyano-O-phenylisourea (0.49 g, 1.14 mmol) and diphenyl cyanocarbonimidate (0.28 g, 1.17 mmol) are stirred in *i*-propyl alcohol (5 mL) for 18 h. The mixture is concentrated *in vacuo* and is diluted with EtOAc (20 mL). The organic phase is washed with 2 N HCl, 1 N NaOH and brine, is dried ($MgSO_4$) and is evaporated. The residue is purified by flash chromatography (silica gel, EtOAc) to provide the intermediate title compound as a white solid (0.33 g, 50%). MS (ES), 574 $[M+H]^+$.

The cis isomer is also isolated (0.1 g, 15%). MS (ES), 574 $[M+H]^+$.

i. N-trans-[{4-(5-Chloro-thiophen-2-yloxy)-acetyl-2-keto-3-(*S*)-methoxymethyl}-piperazin-1-yl]methylcyclohexyl-cyanoguanidine

N-trans-({[4-(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(*S*)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-cyclohexyl)-N'-cyano-O-phenylisourea (0.025 g, 0.04 mmol) is stirred in a 7 N solution of ammonia in methanol (2 mL) for 18 h. The mixture is diluted with EtOAc (20 mL) and is washed with 1 N NaOH and brine. The organic phase is dried ($MgSO_4$) and is evaporated to provide the title compound as a colorless resin (0.014 g, 70%). MS (ES), 497 $[M+H]^+$.

The Following Compounds are also prepared in a similar manner to that described in Example 1282:

Example 1283

N-trans-[{4-(5-Chloro-thiophen-2-yloxy)-acetyl-2-keto-3-(*S*)-methoxymethyl}-piperazin-1-yl]methylcyclohexyl-N',N'-dimethyl-cyanoguanidine: MS (ES), 510 $[M+H]^+$.

Example 1284

N-trans-[{4-(5-Chloro-thiophen-2-yloxy)-acetyl-2-keto-3-(*S*)-methoxymethyl}-piperazin-1-yl]methylcyclohexyl-N'-methyl-cyanoguanidine: MS (ES), 524 $[M+H]^+$.

Example 1285

N-trans-[{4-(5-Chloro-thiophen-2-yloxy)-acetyl-2-keto-3-(*S*)-methoxymethyl}-piperazin-1-yl]methylcyclohexyl-N'-(2-hydroxyethyl)-N'-methyl-cyanoguanidine: MS (ES), 554 $[M+H]^+$.

EXAMPLE 1286 Preparation of 4-[(5-Chlorothiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-cis-(4-morpholin-4-yl-cyclohexylmethyl)-piperazin-2-one
and
4-[(5-Chlorothiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-trans-(4-morpholin-4-yl-cyclohexylmethyl)-piperazin-2-one

A. Dimethoxymethyl-(2,3-dioxa-spiro[4.5]dec-8-ylmethyl)-amine

8-Carboxaldehyde-1,4-dioxa-spiro[4.5]decane (4.4 g, 26 mmol), prepared according to the method of Pearson et al. (*J. Org. Chem.* 62, 1997, 5284), aminoacetaldehyde dimethyl acetal (3.3 g, 0.31 mmol), acetic acid (1.6 g, 0.26 mmol) and sodium cyanoborohydride (2.0 g, 0.31 mmol) are stirred in methanol (140 mL) for 6 h. The methanol is evaporated and the residue is partitioned between ethyl acetate (200 mL) and 1 N NaOH (100 mL). The organic phase is dried (Na_2SO_4) and is evaporated to provide the intermediate title compound as a yellow oil (7.2 g) which is used without further purification. MS (EI), 259 $[M]^+$.

B. {1-[2,2-Dimethoxy-ethyl)-(2,3-dioxa-spiro[4.5]dec-8-ylmethyl)-carbamoyl]-2-(*S*)-methoxyethyl}-carbamic acid benzyl ester

Dimethoxymethyl-(2,3-dioxa-spiro[4.5]dec-8-ylmethyl)-amine (6.6 g, 26 mmol), (*S*)-(2-benzyloxycarbonylamino-3-methoxy)-propionic acid (7.2 g, 28 mmol), [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (12 g, 31 mmol) and N,N-diisopropylethylamine (7.7 g, 60 mmol) are stirred in DMF (200 mL) for 18 h. The DMF is evaporated and the residue diluted with ethyl acetate (200 mL). The organic phase is washed with water (50 mL), 2 N HCl (50 mL), 1 N NaOH (50 mL), is dried ($MgSO_4$) and is evaporated to provide the intermediate title compound as a yellow oil (13 g) which is used without further purification. MS (ES), 495 $[M+H]^+$.

C. 4-(1,4-Dioxa-spiro[4.5]dec-8-ylmethyl)-2-(*S*)-methoxymethyl-3-oxo-3,4-dihydro-2H-pyrazine-1-carboxylic acid benzyl ester

{1-[2,2-Dimethoxy-ethyl)-(2,3-dioxa-spiro[4.5]dec-8-ylmethyl)-carbamoyl]-2-(*S*)-methoxyethyl}-carbamic acid benzyl ester (12.8 g, 26 mmole) and *p*-toluenesulphonic acid monohydrate (0.74 g, 3.9 mmol) are placed in toluene (150 mL) and stirred at 60-70°C for 7 h. The mixture is evaporated and the residue is purified by flash chromatography (silica gel, 2:1 hexanes/ethyl acetate) to provide the intermediate title compound as a clear colorless oil (5.0 g, 45%). MS (ES), 431 $[M+H]^+$.

D. 1-(1,4-Dioxa-spiro[4.5]dec-8-ylmethyl)-2-(*S*)-methoxymethyl-piperazin-2-one

4-(1,4-Dioxa-spiro[4.5]dec-8-ylmethyl)-2-(*S*)-methoxymethyl-3-oxo-3,4-dihydro-2H-pyrazine-1-carboxylic acid benzyl ester (4.7 g, 11 mmol) and 10% Pd on carbon (1.0 g) are stirred in methanol (150 mL) under a hydrogen atmosphere for 18 h. The mixture is filtered through Celite® and is evaporated to provide the intermediate title compound as a clear colorless oil (3.3 g, 11 mmol). MS (EI), 298 $[M]^+$.

E. 4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-(1,4-dioxa-spiro[4.5]dec-8-ylmethyl)-3-(*S*)-methoxymethyl-piperazin-2-one

1-(1,4-Dioxa-spiro[4.5]dec-8-ylmethyl)-2-(*S*)-methoxymethyl-piperazin-2-one (3.3 g, 11 mmol), (5-chloro-thiophen-2-yloxy)-acetic acid (2.1 g, 11 mmol), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (3.9 g, 12 mmol) and triethylamine (3.3 g, 33 mmol) are stirred in DMF (100 mL) for 8 h. The mixture is evaporated and is diluted with ethyl acetate (200 mL). The organic phase is washed with water, 2 N HCl, 1 N NaOH and brine, is dried ($MgSO_4$)

and is evaporated. The residue is purified by flash chromatography (silica gel, 4:1 ethyl acetate/hexanes) to provide the intermediate title compound as a clear colorless oil (2.8 g, 54%). MS (ES), 473 $[M+H]^+$.

F. 4-[(5-Chlorothiophen-2-yloxy)-acetyl]-3-(*S*)-methoxymethyl-1-(4-oxocyclohexylmethyl)-piperazin-2-one

4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-(1,4-dioxa-spiro[4.5]dec-8-ylmethyl)-3-(*S*)-methoxymethyl-piperazin-2-one (2.8 g, 5.9 mmol) is placed in 80:20 acetic acid/water and heated at 65°C for 0.2 h. The mixture is evaporated and is diluted with ethyl acetate (200 mL). The organic phase is washed with 1 N NaOH, is dried ($MgSO_4$) and is evaporated to provide the intermediate title compound as a clear colorless oil (2.4 g, 95%). MS (ES), 429 $[M+H]^+$.

G. 4-[(5-Chlorothiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-cis-(4-morpholin-4-yl-cyclohexylmethyl)-piperazin-2-one
and
4-[(5-Chlorothiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-trans-(4-morpholin-4-yl-cyclohexylmethyl)-piperazin-2-one

4-[(5-Chlorothiophen-2-yloxy)-acetyl]-3-(*S*)-methoxymethyl-1-(4-oxocyclohexylmethyl)-piperazin-2-one (0.07 g, 0.14 mmol), morpholine (0.025 g, 0.28 mmol), acetic acid (0.008 g, 0.14 mmol) and sodium cyanoborohydride (0.01 g, 0.17 mmol) are stirred in methanol (1 mL) for 48 h. The solvent is removed in vacuo and the residue is purified by flash column chromatography (silica gel, 98:2 dichloromethane/methanol) to provide the cis isomer compound as a colorless resin (0.01 g, 15%). MS (ES), 500 $[M+H]^+$.

The trans isomer is also isolated (0.02, g, 29%). MS (ES), 500 $[M+H]^+$.

The following compounds are also prepared in a similar manner to that descroibed in Example 1286.

Example 1287 4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-cis-{4-[(2-hydroxy-ethyl)-methyl-1-amino]-cyclohexylmethyl)-3-(*S*)-methoxymethyl-piperazin-2-one: MS (ES), 488 $[M+H]^+$.

EXAMPLE 1288 4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-trans-{4-[(2-hydroxy-ethyl)-methyl-1-amino]-cyclohexylmethyl)-3-(*S*)-methoxymethyl-piperazin-2-one:
MS (ES), 488 $[M+H]^+$.

EXAMPLE 1289 4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-cis-{4-[2-(R,S)-(1-methyl-pyrrolidin-2-yl)-ethylamino]-cyclohexylmethyl}-piperazine-2-one: MS (ES), 541 $[M+H]^+$.

EXAMPLE 1290 4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-trans-{4-[2-(R,S)-(1-methyl-pyrrolidin-2-yl)-ethylamino]-cyclohexylmethyl}-piperazine-2-one: MS (ES), 541 $[M+H]^+$.

EXAMPLE 1291 4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-cis-[4-(2-pyridin-2-yl-ethylamino)-cyclohexylmethyl]-piperazin-2-one: MS (ES), 535 $[M+H]^+$.

EXAMPLE 1292 4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-trans-[4-(2-pyridin-2-yl-ethylamino)-cyclohexylmethyl]-piperazin-2-one: MS (ES), 535 $[M+H]^+$.

EXAMPLE 1293 4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-cis-[4-(2-dimethylamino-ethylamino)-cyclohexylmethyl]-3-(S)-methoxymethyl-piperazin-2-one: MS (ES), 501 $[M+H]^+$.

EXAMPLE 1294 4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-trans-[4-(2-dimethylamino-ethylamino)-cyclohexylmethyl]-3-(S)-methoxymethyl-piperazin-2-one: MS (ES), 501 $[M+H]^+$.

EXAMPLE 1295 4-(4-cis-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-piperazine-1-carboxylic acid ethyl ester: MS (ES), 571 $[M+H]^+$.

EXAMPLE 1296 4-(4-trans-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-piperazine-1-carboxylic acid ethyl ester: MS (ES), 571 $[M+H]^+$.

EXAMPLE 1297 4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-cis-([4-(4-hydroxy-piperidin-1-yl)-cyclohexylmethyl]-3-(S)-methoxymethyl-piperazin-2-one: MS (ES), 514 $[M+H]^+$.

EXAMPLE 1398 4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-trans-([4-(4-hydroxy-piperidin-1-yl)-cyclohexylmethyl]-3-(S)-methoxymethyl-piperazin-2-one: MS (ES), 514 $[M+H]^+$.

EXAMPLE 1399 1-cis-(4-Azepan-1-yl-cyclohexylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one MS (ES), 512 $[M+H]^+$.

EXAMPLE 1300 1-trans-(4-Azepan-1-yl-cyclohexylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one:
MS (ES), 512 $[M+H]^+$.

EXAMPLE 1301 4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-cis-{4-[(pyridin-2-ylmethyl)-amino]-cyclohexylmethyl}-piperazin-2-one MS (ES), 521 $[M+H]^+$.

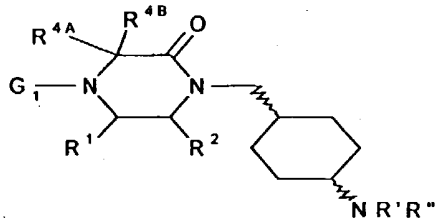
EXAMPLE 1302 4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-trans-{4-[(pyridin-2-ylmethyl)-amino]-cyclohexylmethyl}-piperazin-2-one:
MS (ES), 521 $[M+H]^+$.

EXAMPLE 1303 4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-cis-(4-phenylamino-cyclohexylmethyl)-piperazin-2-one: MS (ES), 506 $[M+H]^+$.

EXAMPLE 1304 4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-trans-(4-phenylamino-cyclohexylmethyl)-piperazin-2-one:
MS (ES), 506 $[M+H]^+$.

EXAMPLE 1305 4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-cis-{4-[2-(2-hydroxy-ethoxy)-ethylamino]-cyclohexylmethyl}-3-(S)-methoxymethyl-piperazin-2-one: MS (ES), 518 $[M+H]^+$.
and
EXAMPLE 1306 4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-trans-{4-[2-(2-hydroxy-ethoxy)-ethylamino]-cyclohexylmethyl}-3-(S)-methoxymethyl-piperazin-2-one:
MS (ES), 518 $[M+H]^+$.

Similarly, additional 1-(alkyl,arly)amino-4-methylcyclohexyl compounds can be prepared from intermediates having a structure



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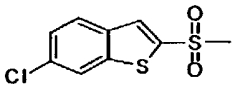
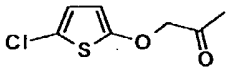
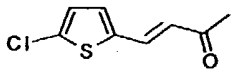
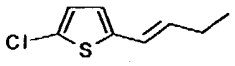
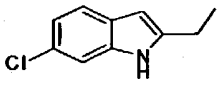
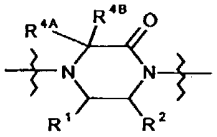
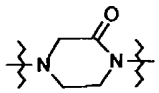
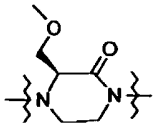
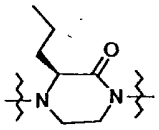
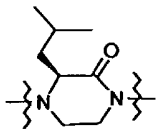
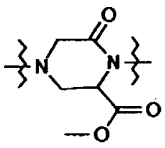
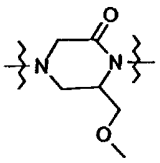
 ,  ,  ,

 , and  ;

 includes but is not limited to

 ,  , 

 ,  , and  ; and

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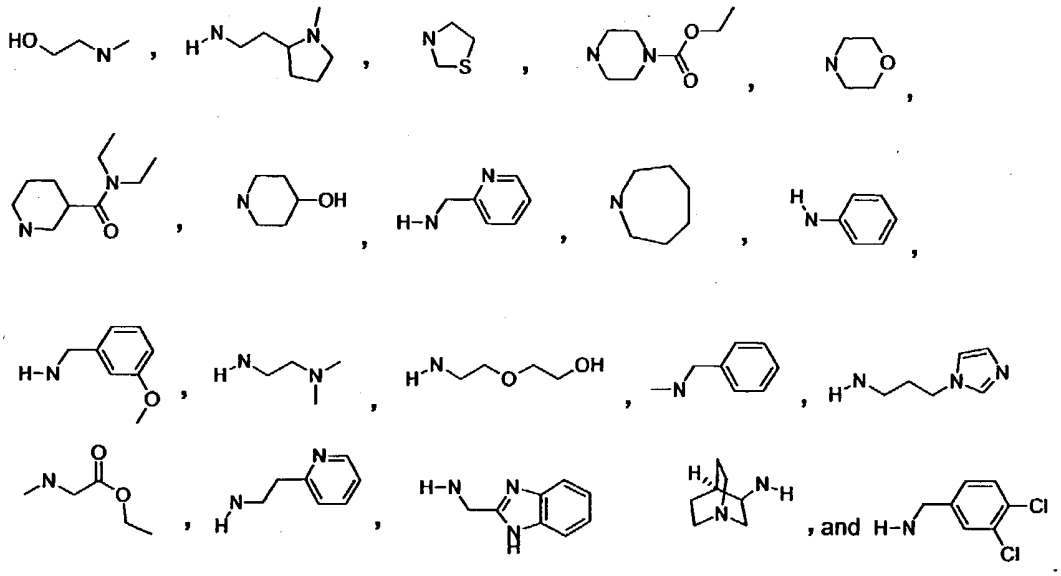


EXAMPLE 1307 4-[(5-Chlorothiophen-2-yloxy)-acetyl]-1-[(2-{[N,N-dimethylaminoethyl]-amino}-pyrimidin-5-yl)-methyl]-3-(*S*)-methoxymethyl-piperazine-2-one

A. 5-hydroxymethyl-2-methylthiopyrimidine

To a solution of 2-methylthiopyrimidine-5-carboxaldehyde (1.35 g, 8.7 mmol), prepared according to the method of Gupton et al. (*J. Het. Chem.* 28, 1991, 1281), in methanol (1 mL) at 0°C is added sodium borohydride (0.3 g, 7.9 mmol). The mixture is stirred for 0.5 h and is concentrated *in vacuo*. The residue is partitioned between EtOAc and 1 N NaOH. The organic phase is dried ($MgSO_4$) and is evaporated to yield the intermediate title compound as a yellow solid (1.18 g, 87%). MS (ES), 157 $[M+H]^+$.

B. 5-bromomethyl-2-methylthiopyrimidine

5-hydroxymethyl-2-methylthiopyrimidine (0.1 g, 0.61 mmol), triphenylphosphine (0.45 g, 1.7 mmol) and carbon tetrabromide (0.28 g, 0.85 mmol) are stirred in benzene (5 mL) for 24 h. The mixture is evaporated and the residue is purified by flash chromatography (silica gel, 4:1 hexanes/ethyl acetate) to provide the intermediate title compound as a white solid (0.08 g, 61%). MS (ES), 219/221 $[M+H]^+$ (Br).

C. 4-benzyloxycarbonyl-3-(*S*)-methoxymethyl-1-[(2-methylthiopyrimidin-5-yl)-methyl]-piperazine-2-one

4-Benzyloxycarbonyl-3-(*S*)-methoxymethyl-piperazine-2-one (0.1 g 0.37 mmol), 5-bromomethyl-2-methylthiopyrimidine (0.08 g, 0.37 mmol) and tetra-*n*-butylammonium bromide

(0.06 g, 0.19 mmol) are placed in dichloromethane (1 mL) and 50% aqueous NaOH (0.03 mL) and stirred for 4 h. The mixture is diluted with water and is extracted with dichloromethane (2 X 20 mL). The combined organic extracts are dried ($MgSO_4$) and are evaporated. The residue is purified by flash chromatography (silica gel, 98:2 dichloromethane/methanol) to provide the intermediate title compound as a colorless oil (0.05 g, 33%). MS (ES), 417 $[M+H]^+$.

D. 4-benzyloxycarbonyl-1-[(2-{[N,N-dimethylaminoethyl]-amino}-pyrimidin-5-yl)-methyl]-3-(*S*)-methoxymethyl-piperazine-2-one

4-benzyloxycarbonyl-3-(*S*)-methoxymethyl-1-[(2-methylthiopyrimidin-5-yl)-methyl]-piperazine-2-one (0.045 g, 0.11 mmol) is dissolved in dichloromethane (3 mL) and cooled to -78°C. 57-86% 3-Chloroperoxybenzoic acid (0.095 g, 0.33 mmol) is added and the mixture is warmed to room temperature. The mixture is diluted with dichloromethane (20 mL) and is washed with dilute aqueous Na_2CO_3. The organic phase is dried (Na_2SO_4) and is evaporated. The crude residue is used without further purification. MS (ES), 449 $[M+H]^+$. The residue is placed in DMF (1 mL) and N,N-dimethylethylamine (0.05 g, 0.6 mmol) is added. The mixture is stirred for 4 h and is concentrated *in vacuo*. Purification by flash chromatography (silica gel, 9:1 dichloromethane/methanol) provided the intermediate title compound as a colorless resin (0.01 g, 20%). MS (ES), 457 $[M+H]^+$.

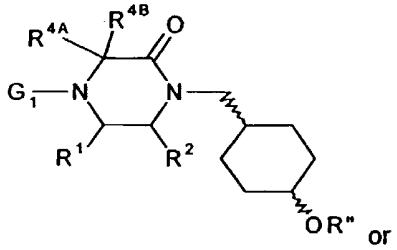
E. 1-[(2-{[N,N-dimethylaminoethyl]-amino}-pyrimidin-5-yl)-methyl]-3-(*S*)-methoxymethyl-piperazine-2-one

4-Benzyloxycarbonyl-1-[(2-{[N,N-dimethylaminoethyl]-amino}-pyrimidin-5-yl)-methyl]-3-(*S*)-methoxymethyl-piperazine-2-one (0.01 g, 0.02 mmol) and 10% Pd on carbon (0.01 g) are stirred in acetic acid (3 mL) under a hydrogen atmosphere for 18 h. The mixture is filtered through Celite® and is evaporated to provide the intermediate title compound as a clear colorless oil (0.002 g). MS (ES), 323 $[M+H]^+$.

F. 4-[(5-Chlorothiophen-2-yloxy)-acetyl]-1-[(2-{[N,N-dimethylaminoethyl]-amino}-pyrimidin-5-yl)-methyl]-3-(*S*)-methoxymethyl-piperazine-2-one

The title compound can be prepared by placing 1-[(2-{[N,N-dimethylaminoethyl]-amino}-pyrimidin-5-yl)-methyl]-3-(*S*)-methoxymethyl-piperazine-2-one, (5-chloro-thiophen-2-yloxy)-acetic acid, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate and triethylamine in DMF and stirring 8-16 h. The mixture is evaporated and is diluted with ethyl acetate. The organic phase is washed with water, 2 N HCl, 1 N NaOH and brine, is dried ($MgSO_4$) and is evaporated. The residue is purified by flash chromatography (silica gel, 4:1 ethyl acetate/hexanes) to provide the title compound.

Similarly, 2-amino & alkoxy-4&5-substituted-methylpyrimidinyl compounds can be prepared from intermediates having a structure



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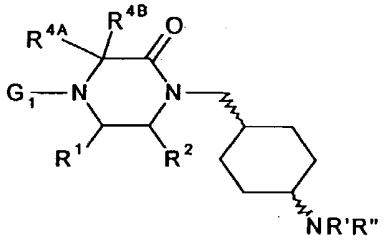

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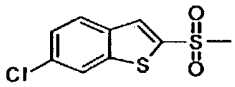

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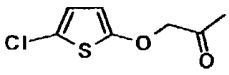

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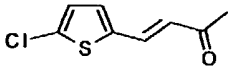

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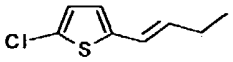

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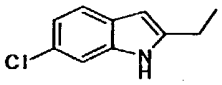

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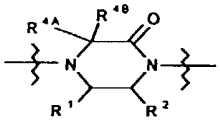

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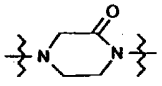

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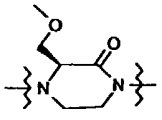

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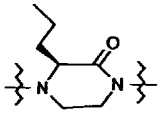

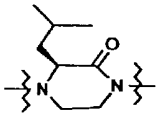

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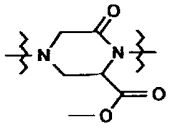

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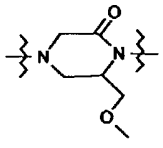

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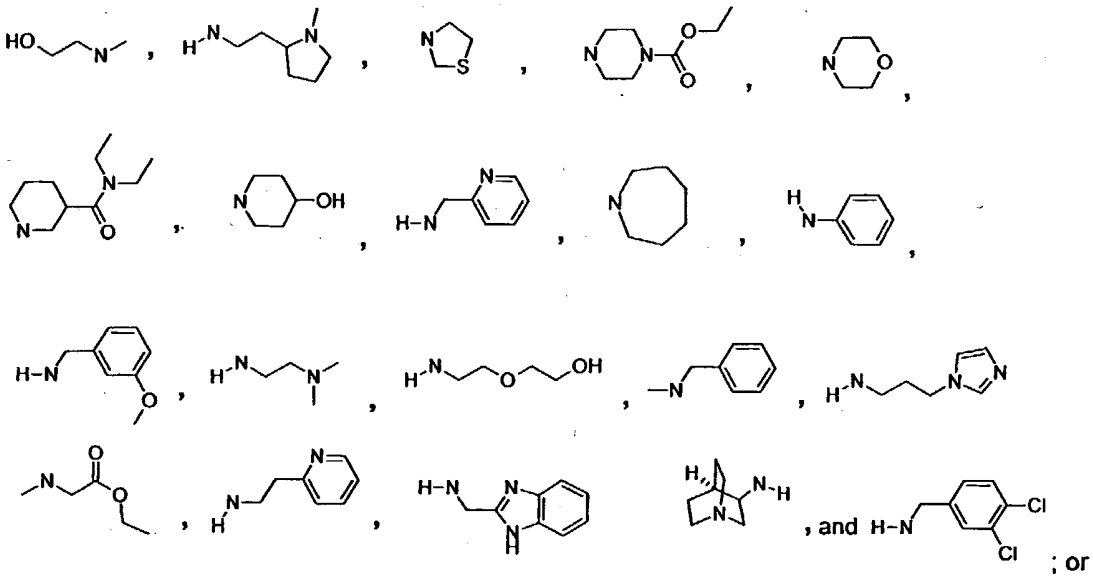

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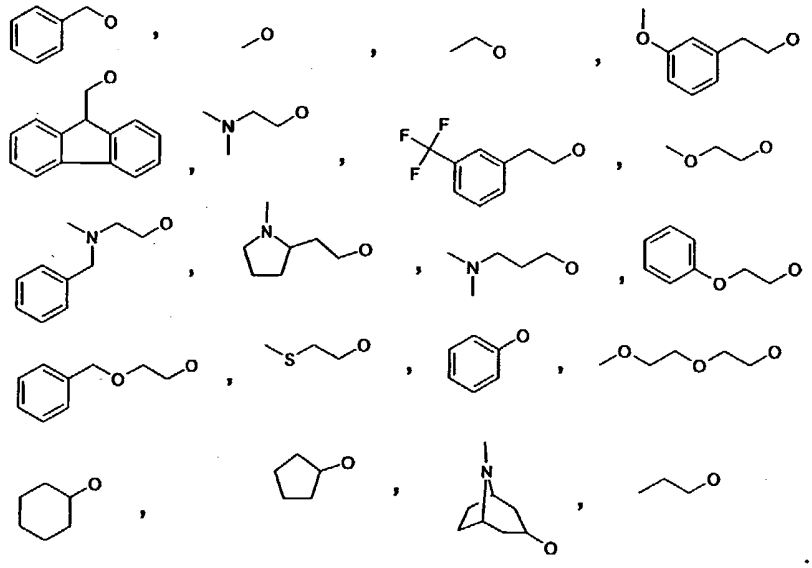


EXAMPLE 1308. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-allyl]-piperazine-2,3-dione.

A. Methyl 2-amino -4-hydroxymethlybenzoate.

To a solution of 16.0 g (76.6 mmole) of dimethyl aminoterephthalate in 200 ml of anhydrous THF cooled to -78°C is added 250 ml (250 mmole) of 1 M Super Hydride dropwise over 1 hour. The mixture is stirred for an additional 1.5 hours warming to 0°C (a little starting material on TLC is observed). The mixture is poured into 300 ml of cold water and extracted with ethyl acetate. The organic layer is washed with water and the two layers are allowed to

stand for 30 minutes. The organic layer is dried over $MgSO_4$ and filtered. The filtrate is evaporated. The residue is dissolved in ethyl acetate and the solution is poured over a Buchner funnel containing silica gel, using 150 ml of ethyl acetate to wash the funnel. The filtrate is evaporated. The residue is dissolved in the minimum amount of ethyl acetate and the solution is diluted to the cloudy point with hexane. Additional hexane is added as the product precipitates. A total of 100 ml of hexane is added and the solid is collected and vacuum dried to give 8.4 g of the title intermediate material, 98-100°C mp; 61% yield. ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.82 (d, 1H), 6.67 (s, 1H), 6.60 (d, 1H), 5.75 (bs, 2H), 4.62 (s, 2H), 3.86 (s, 3H), 1.83 (bs, 1H). EI MS, $[M]^+$=181.

B. 7-Hydroxymethlyquinazolin-4-one.

A mixture of 2.0 g (19.1 mmole) of methyl 2-amino-4-hydroxymethlybenzoate in 4 ml of formamide is heated in an oil bath of 180°C for three hours. The mixture is cooled and triturated with 70 ml of boiling ethyl acetate. The ethyl acetate is then decanted from the dark oil and cooled in a freezer overnight to precipitate 0.7 g 205-12°C mp; 40% yield. ^{1}H NMR (d_6-DMSO, 300MHz) δ 8.08 (s, 1H), 8.06 (d, 1H), 7.60 (s, 1H), 7.45 (d, 1H), 5.48 (bs, 1H), 4.65 (s, 2H), 3.35 (bs, 1H). EI MS, $[M]^+$=176.

C. 4-Chloro-7-chloromethylquinazoline.

A mixture of 2.0 g (11.3 mmole) of 7-hydroxymethylquinazolin-4-one in 25 ml of phosphorus oxychloride is heated under reflux for 30 minutes. A very thick mixture is formed and the heating is continued for an additional 1.5 hours to give a solution. The phosphorus oxychloride is evaporated in a rotary evaporator and the residue is poured into ice water. The mixture is extracted with ether. The ether is dried over $MgSO_4$, filtered, and the filtrate evaporated. The residue is treated with 10 ml of ether and filtered. The filtrate is evaporated to afford 0.8 g of intermediate product which is used directly in the next step without further purification; 33% yield. ^{1}H NMR ($CDCl_3$, 300MHz) δ 9.07 (s, 1H), 8.30 (d, 1H), 8.06 (s, 1H), 7.78 (d, 1H), 4.78 (s, 2H). EI MS, $[M]^+$=212, 214, 216 (Cl_2 pattern).

D. 4-Amino-7-chloromethylquinazoline.

To 15 ml of a saturated ethanolic ammonia solution is added 1.0 g (4.7 mmole) of 4-chloro-7-chloromethylquinazoline. The mixture is stirred at room temperature overnight. The precipitate which forms is collected to give 0.7 g of the title intermediate product, mp>300°C; 77% yield. ^{1}H NMR (d_6-DMSO, 300MHz) δ 8.38 (s, 1H), 8.20 (d, 1H), 7.78 (bs, 2H), 7.70 (s, 1H), 7.51 (d, 1H), 4.92 (s, 2H). EI MS, $[M]^+$=193, 195 (Cl pattern).

E. 3-(4-Chloro-phenyl)-(E)-propenal.

To a solution of 3-(4-chloro-phenyl)-prop-2-(E)-en-1-ol (2.33 g, 13.8 mmol, prepared as described in *J.Med. Chem.* 1997, 1827) in 50 ml of CH_2Cl_2 is added activated manganese (IV) oxide (4.80 g , 55.3 mmol) in three portions over 3 hours and the resulting suspension is stirred at room temperature overnight. After filtration through a pad of celite and concentration *in vacuo*, the crude residue is purified by column chromatography eluting with 10% EtOAc/hexanes to provide the title intermediate compound (0.80 g , 4.80 mmol) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300MHz) δ 9.71 (d, 1H), 7.48 (m, 3H), 7.41 (dd, 2H), 6.68 (dd, 1H).

F. {2-[3-(4-Chloro-phenyl)-allylamino]-ethyl}-carbamic acid tert-butyl ester.

To a solution of N-Boc-ethylenediamine (0.63 g, 4.80 mmol) in 20mL of MeOH is added 3-(4-chloro-phenyl)-(E)-propenal (0.80 g, 4.80 mmol). After stirring for 3 hours at room temperature over 4A molecular sieves, $NaBH_4$ (0.19 g, 5.00 mmol) is added. The reaction mixture is stirred for 16 hours, then diluted with EtOAc and filtered through Celite plug. The solution is concentrated under reduced pressure. The residue is partitioned between EtOAc and H_2O and the layers are separated. The aqueous layer is extracted with EtOAc. The combined organic layers are washed with H_2O, brine, then dried over $MgSO_4$, filtered and concentrated. The crude title product is purified by column chromatography, eluting with a gradient of 25% EtOAc/CH_2Cl_2 to 50% EtOAc/CH_2Cl_2 to provide the title intermediate compound (0.80g, 2.57 mmol). ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.26 (s, 4H), 6.49 (d, 1H), 6.23 (dt, 1H), 4.96 (bs, 1H), 3.40 (m, 2H), 3.25 (m,, 2H), 2.76 (m, 2H), 1.60 (bs, 1H), 1.45 (s, 9H).

G. N-(2-tert-Butoxycarbonylamino-ethyl)-N-[3-(4-chloro-phenyl)-allyl]-oxalamic acid methyl ester.

To a solution of {2-[3-(4-chloro-phenyl)-allylamino]-ethyl}-carbamic acid tert-butyl ester (0.80 g, 2.57 mmol) in 15 ml of CH_2Cl_2 at 0°C is added triethylamine (0.54 mL , 3.85 mmol) and methyl chlorooxoacatate (0.25 mL, 2.70 mmol). The resulting mixture is stirred at 0°C for 1 h, then at room temperature for 1 h. The solution is partitioned between EtOAc and H_2O and the layers separated. The organic layer is washed with 1N HCl solution, H_2O, saturated $NaHCO_3$ solution and brine, then dried over $MgSO_4$, filtered and concentrated. The crude product is purified by column chromatography eluting with 25% EtOAc/CH_2Cl_2 to provide the title intermediate compound (0.98g, 2.47 mmol). ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.31 (m, 4H), 6.55 (dd, 1H), 6.14 (m, 1H), 4.88 (bs, 1H), 4.21, 4.10 (d, 2H, rotamers), 3.91, 3.86 (s, 3H, rotamers), 3.55, 3.44 (m, 2H, rotamers), 3.36 (m, 2H), 1.43 (s, 9H).

H. 1-[3-(4-Chloro-phenyl)-allyl]-piperazine-2,3-dione.

A solution of N-(2-tert-butoxycarbonylamino-ethyl)-N-[3-(4-chloro-phenyl)-allyl]-oxalamic acid methyl ester (0.49 g, 1.23 mmol) in 6 mL of EtOAc at 0 °C is saturated with HCl gas. The ice-bath is removed and the solution is stirred at room temperature for 30 min as a white

precipitate forms after about 5-10 min. After this time, the solution is concentrated to a white solid (0.41 g). The crude amine salt is suspended in 6 mL CH_2Cl_2 and 1.5 mL of MeOH. Triethylamine (0.5 mL, 3.53 mmol) is added and the resulting solution is stirred at room temperature overnight. The solution is concentrated under reduced pressure and partitioned between CH_2Cl_2 and H_2O. The aqueous layer is basified with 0.5N NaOH. The organic layer is washed with H_2O, brine, then dried over $MgSO_4$, filtered and concentrated. The title intermediate compound is obtained as a white solid (0.32 g, 1.21 mmol). ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.82 (bs, 1H), 7.30 (s, 4H), 6.56 (d, 1H), 6.14 (dt, 1H), 4.27 (d, 2H), 3.58 (m, 4H).

I. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-allyl]-piperazine-2,3-dione.

To a solution of 1-[3-(4-chloro-phenyl)-allyl]-piperazine-2,3-dione (60 mg, 0.23 mmol) in 1.5 mL of DMF is added NaH (10 mg of a 60% dispersion in mineral oil, 0.24 mmol). The mixture is heated at 55°C for 20 min. To the solution is added 4-amino-7-chloromethyl-quinazoline (49 mg, 0.25 mmol), and the resulting mixture is heated at 55°C for 20 min as a white precipitate is formed. After this time, reaction mixture is quenched with a few drops of H_2O and MeOH, then concentrated. The crude product is purified by RP-HPLC, eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 70% CH_3CN/H_2O (0.1% TFA) over 30 minutes, and the appropriate product fractions are combined and lyopholized to provide the title compound (56 mg, 0.10 mmol) as a white solid. ^{1}H NMR (d_6-DMSO, 300 MHz) δ 9.78 (bs, 2H), 8.83 (s, 1H), 8.40 (s, 1H), 7.72 (d, 1H), 7.65 (s, 1H), 7.49 (d, 2H), 7.38 (d, 2H), 6.61 (d, 1H), 6.30 (dt, 1H), 4.80 (s, 2H), 4.18 (d, 2H), 3.59 (m, 4H). ISP MS, $[M+H]^+$=422.

EXAMPLE 1328. 1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-(4-pyridin-4-yl-benzyl)-piperazine-2,3-dione.

A. {2-[3-(5-Chloro-thiophen-2-yl)-allylamino]-ethyl}-carbamic acid tert-butyl ester.

The title compound is prepared as described in EXAMPLE 1306, Part F from 3-(5-chloro-thiophen-2-yl)-(E)-propenal. ^{1}H NMR ($CDCl_3$, 300MHz) δ 6.77 (d, 1H), 6.67 (d, 1H), 6.52 (d, 1H), 5.99 (dt, 1H), 4.95 (bs, 1H), 3.37 (m, 2H), 3.24 (m, 2H), 2.76 (m, 2H), 1.48 (bs, 1H), 1.45 (s, 9H).

B. N-1-[3-(5-Chloro-thiophen-2-yl)-allylamino]-ethane-1,2-diamine hydrochloride.

A solution of {2-[3-(5-chloro-thiophen-2-yl)-allylamino]-ethyl}-carbamic acid tert-butyl ester (0.11 g, 0.35 mmol) in 20 mL of EtOAc at 0 °C is saturated with HCl gas. The ice-bath is removed and the solution is stirred at room temperature for 1 h. After this time, the solution is concentrated to a white solid (0.41 g). The title compound is obtained as a white solid (0.07 g, 0.27 mmol) and used as is in the following step. ^{1}H NMR ($CDCl_3$, 300MHz) δ 6.76 (d, 1H), 6.68 (d, 1H), 6.54 (d, 1H), 6.01 (dt, 1H), 3.38 (m, 2H), 2.82 (m, 2H), 2.71 (m, 2H), 1.40 (bs, 3H).

C. N-[3-(5-Chloro-thiophen-2-yl)-allyl]-N'-(4-pyridin-4-yl-benzyl)-ethane-1,2-diamine.

To a solution of N-1-[3-(5-chloro-thiophen-2-yl)-allylamino]-ethane-1,2-diamine hydrochloride (0.07 g, 0.27 mmol) in 10mL of MeOH is added 4-pyridin-4-yl-benzaldehyde (0.05 g, 0.27 mmol). After stirring for 16 h at room temperature over 4A molecular sieves, $NaBH_4$ (0.01 g, 0.27 mmol) is added. The reaction mixture is stirred for 5 h, filtered through a Celite plug and concentrated. The residue is partitioned between EtOAc and H_2O and the layers are separated. The aqueous layer is extracted with EtOAc. The combined organic layers are washed with H_2O (3X), brine, then dried over $MgSO_4$, filtered and concentrated. The crude material is purified by column chromatography, eluting with a gradient of 5% MeOH/CH_2Cl_2 to 10% MeOH/CH_2Cl_2 with 2% NH_4OH present to provide the title compound (0.042g, 0.11 mmol). ^1H NMR ($CDCl_3$, 300MHz) δ 8.65 (d, 2H), 7.61, (d, 2H), 7.50 (d, 2H), 7.45 (d, 2H), 6.76 (d, 1H), 6.67 (d, 1H), 6.52 (d, 1H), 6.00 (dt, 1H), 3.38 (s, 2H), 3.35 (d, 2H), 2.78 (s, 4H), 1.78 (bs, 2H).

D. 1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-(4-pyridin-4-yl-benzyl)-piperazine-2,3-dione.

To a solution of N-[3-(5-Chloro-thiophen-2-yl)-allyl]-N'-(4-pyridin-4-yl-benzyl)-ethane-1,2-diamine (0.037 g, 0.10 mmol) in 1.5 ml of EtOH is added dimethyl oxalate (0.012 g, 0.10 mmol). The resulting mixture is stirred at room temperature for 16 h, then heated at 50 °C for 16 h. The solution is concentrated. The crude product is purified by column chromatography, eluting with a gradient of 5% MeOH/CH_2Cl_2 to 10% MeOH/CH_2Cl_2 to provide the title compound as a white solid (0.024 g, 0.04 mmol). ^1H NMR ($CDCl_3$, 300MHz) δ 8.68 (d, 2H), 7.63, (d, 2H), 7.50 (m, 2H), 7.43 (d, 2H), 6.79 (d, 1H), 6.672(d, 1H), 6.59 (d, 1H), 5.87 (dt, 1H), 4.76 (s, 2H), 4.20 (d, 2H), 3.48 (s, 4H). ISP MS, $[M+H]^+$=438, 440, Cl pattern.

The following 2,3-diketopiperazine compounds are prepared in a similar fashion using the procedures described above.

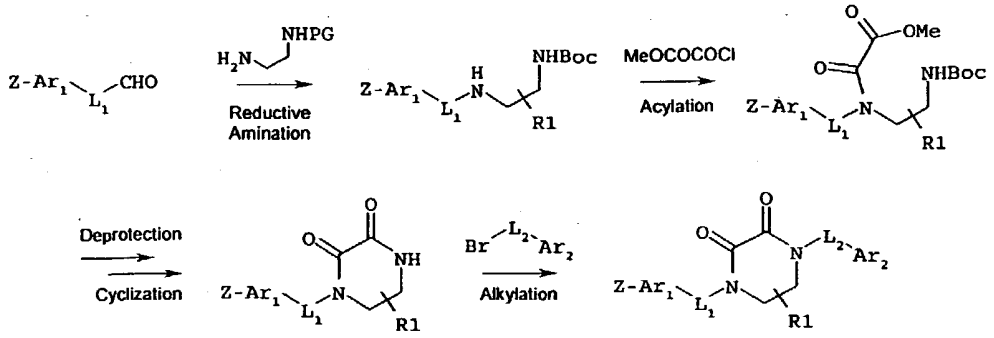
Example	Name	m/z [M+H]
1309	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-yl-methyl)-piperazine-2,3-dione	ISP-452, Cl
1310	1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-allyl]-piperazine-2,3-dione	ISP-421, Cl
1311	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-ylmethyl)-piperazine-2,3-dione	ISP-484
1312	1-(3-carbamimidoyl-benzyl)-4-(4-carbamimidoyl-benzyl)-2,3 dioxopiperizine	ISP-379

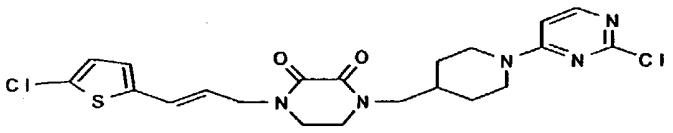
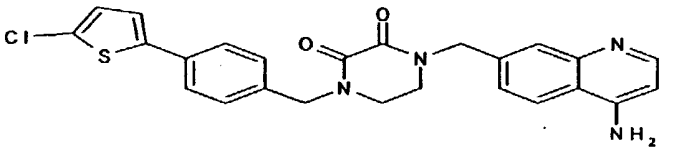
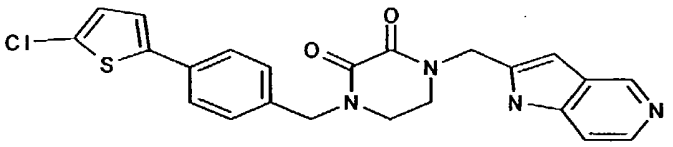
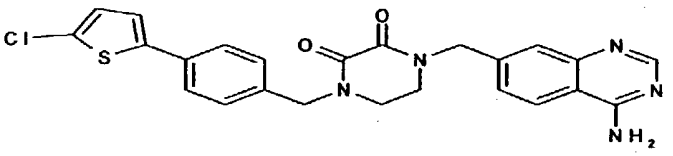
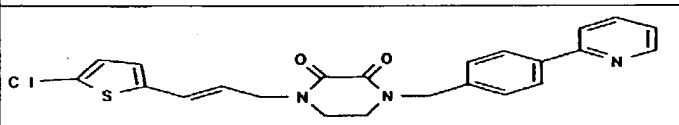
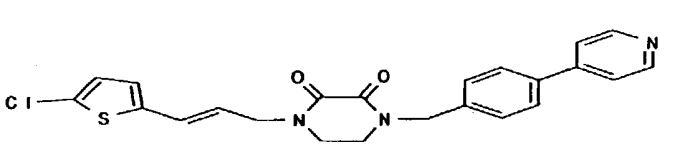
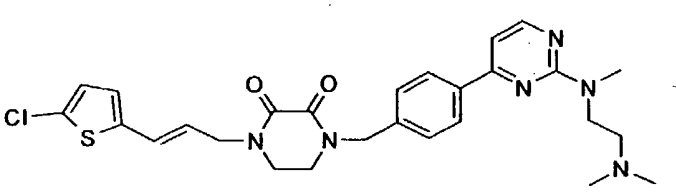
1313	Bis-1,4-(3-carbamimidoyl-benzyl)-2,3-dioxopiperizine	ISP-379
1314	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-allyl]-piperazine-2,3-dione	
1315	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazine-2,3-dione	ISP-428, Cl
1316	1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-yl-methyl)-piperazine-2,3-dione	
1317	1-(4-Amino-quinolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-ylmethyl)-piperazine-2,3-dione	
1318	1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazine-2,3-dione	ISP-427, Cl
1319	1-[3-(3-chloro-phenyl)-allyl]-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2,3-dione	
1320	1-[3-(4-chloro-phenyl)-allyl]-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2,3-dione	ISP-395, Cl
1321	1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2,3-dione	ISP-401, Cl
1322	1-(6-chloro-benzo[b]thiophen-2-yl-methyl)-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2,3-dione	
1323	1-(5'-chloro-[2,2']bithiophenyl-5-ylmethyl)-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2,3-dione	
1324	1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)-piperazine-2,3-dione	
1325	1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-(thieno[3,2-b]pyridin-2-ylmethyl)-piperazine-2,3-dione	
1326	1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-(4-pyridin-2-yl-benzyl)-piperazine-2,3-dione	ISP-438, Cl
1327	1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-[4-(1-hydroxy-pyridin-2-yl)-benzyl]-piperazine-2,3-dione	ISP-454, Cl
1328	1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-(4-pyridin-4-yl-benzyl)-piperazine-2,3-dione	ISP-438, Cl
1329	1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-[4-(1-hydroxy-pyridin-4-yl)-benzyl]-piperazine-2,3-dione	
1330	1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-[4-(6-methoxy-pyridin-3-yl)-	ISP-468

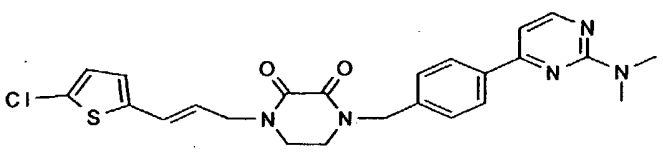
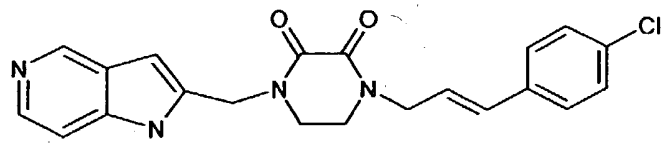
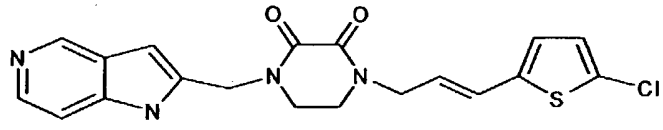
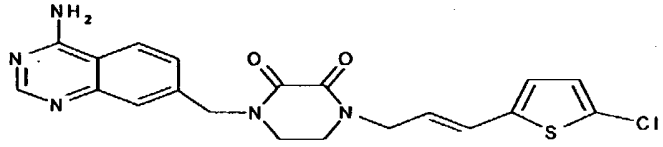
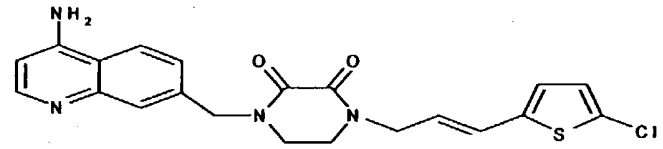
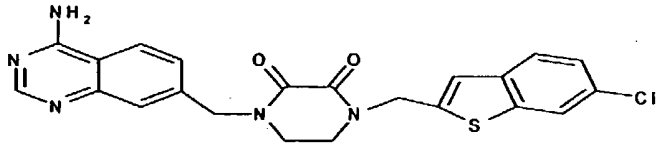
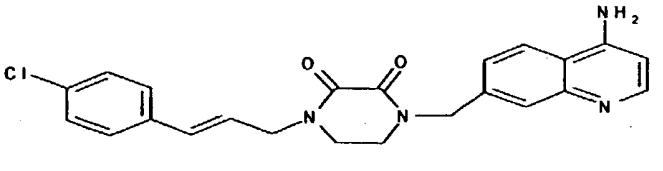
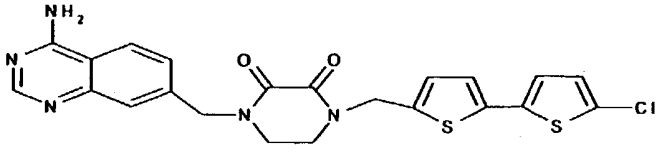
	benzyl]-piperazine-2,3-dione	
1331	1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazine-2,3-dione	ISP-454
1332	1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-[4-(2-dimethylamino-pyrimidin-4-yl)-benzyl]-piperazine-2,3-dione	ISP-482, Cl
1333	1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-(4-{2-[(2-dimethylamino-ethyl)-methyl-amino]-pyrimidin-4-yl}-benzyl)-piperazine-2,3-dione	ISP-539, Cl
1334	1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-[4-(2-dimethylamino-pyrimidin-4-yl)-cyclohexymethyl]-piperazine-2,3-dione	
1335	1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-(4-{2-[(2-dimethylamino-ethyl)-methyl-amino]-pyrimidin-4-yl}-cyclohexylmethyl)-piperazine-2,3-dione	
1336	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-5-methyl-piperazine-2,3-dione	
1337	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-5-ethyl-piperazine-2,3-dione	
1338	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-5-propyl-piperazine-2,3-dione	
1339	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-5-butyl-piperazine-2,3-dione	
1340	4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(5-chloro-thiophen-2-yl)-allyl]-5-(S)-isopropyl-piperazine-2,3-dione	ISP-470, Cl
1341	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-5-isobutyl-piperazine-2,3-dione	
1342	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-5-methoxymethyl-piperazine-2,3-dione	
1343	4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(5-chloro-thiophen-2-yl)-allyl]-5,6-dioxopiperazine-2-carboxylic acid	
1344	4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(5-chloro-thiophen-2-yl)-allyl]-5,6-dioxopiperazine-2-carboxylic acid methyl ester	
1345	4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(5-chloro-thiophen-2-yl)-allyl]-5,6-dioxopiperazine-2-carboxylic acid amide	
1346	4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(5-chloro-thiophen-2-yl)-allyl]-5,6-dioxopiperazine-2-carboxylic acid methyl amide	
1347	1-[4-(2-Chloro-pyrimidin-4-yl)-benzyl]-4-[3-(5-chloro-thiophen-2-yl)-	ISP-473,

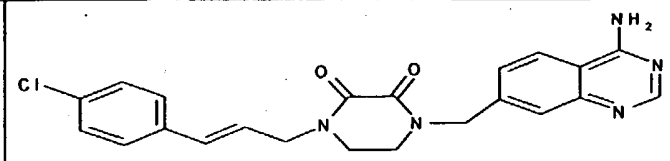
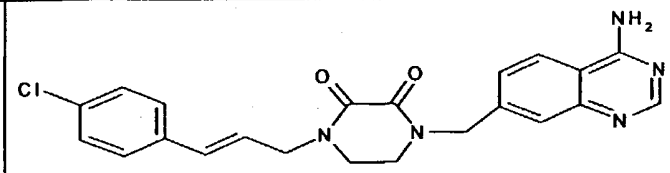
	allyl]-piperazine-2,3-dione	Cl
1348	1-(4-Amino-quinazolin-7-ylmethyl)-4-[4-(5-chloro-thiophen-2-yl)-benzyl]-piperazine-2,3-dione	ISP-478, Cl
1349	1-[4-(5-Chloro-thiophen-2-yl)-benzyl]-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2,3-dione	ISP-451, Cl
1350	1-(4-Amino-quinolin-7-ylmethyl)-4-[4-(5-chloro-thiophen-2-yl)-benzyl]-piperazine-2,3-dione	ISP-477, Cl
1351	1-[1-(2-Chloro-pyrimidin-4-yl)-piperidin-4-ylmethyl]-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazine-2,3-dione	ISP-480, Cl
1352	1-[3-(5-Chloro-thiophen-2-yl)-allyl]-5-(S)-isopropyl-4-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-piperazine-2,3-dione	ISP-487, Cl
1353	1-[3-(5-Chloro-thiophen-2-yl)-allyl]-4-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-piperazine-2,3-dione	ISP-445, Cl
1354	1-[3-(5-Chloro-thiophen-2-yl)-allyl]-4-(4-pyridin-3-yl-benzyl)-piperazine-2,3-dione	ISP-438, Cl
1355	1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(4-pyridin-4-yl-benzyl)-piperazine-2,3-dione	ISP-479, Cl
1356	1-[4-(6-Amino-pyridin-3-yl)-benzyl]-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazine-2,3-dione	ISP-453, Cl
1357	1-[3-(5-Chloro-thiophen-2-yl)-allyl]-4-[4-(1-oxy-pyridin-3-yl)-benzyl]-piperazine-2,3-dione	ISP-454, Cl
1358	1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(S)-isopropyl-4-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-piperazine-2,3-dione	ISP-528, Cl
1359	1-[3-(5-Chloro-thiophen-2-yl)-allyl]-5-(S)-isopropyl-4-(4-pyrimidin-4-yl-benzyl)-piperazine-2,3-dione	ISP-481, Cl
1360	1-[3-(5-Chloro-thiophen-2-yl)-allyl]-4-(4-pyrimidin-4-yl-benzyl)-piperazine-2,3-dione	ISP-439, Cl
1361	1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-piperazine-2,3-dione	ISP-469, Cl

The following 2,3-diketopiperazine compounds are prepared in a similar fashion as in example 1308 and outlined in the following reaction scheme.

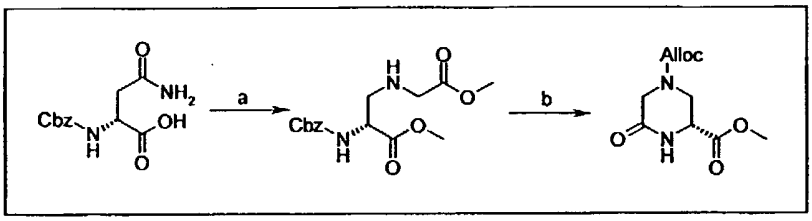


Example	structure	formula	molecular weight
1362		$C_{21}H_{23}Cl_2N_5O_2S$	480,42
1363		$C_{25}H_{21}ClN_4O_2S$	476,99
1364		$C_{23}H_{19}ClN_4O_2S$	450,95
1365		$C_{24}H_{20}ClN_5O_2S$	477,98
1366		$C_{23}H_{20}ClN_3O_2S$	437,95
1367		$C_{23}H_{20}ClN_3O_2S$	437,95
1368		$C_{27}H_{31}ClN_6O_2S$	539,1

1369		$C_{24}H_{24}ClN_5O_2S$	482,01
1370		$C_{21}H_{19}ClN_4O_2$	394,86
1371		$C_{19}H_{17}ClN_4O_2S$	400,88
1372		$C_{20}H_{18}ClN_5O_2S$	427,91
1373		$C_{21}H_{19}ClN_4O_2S$	426,92
1374		$C_{22}H_{18}ClN_5O_2S$	451,93
1375		$C_{23}H_{21}ClN_4O_2$	420,89
1376		$C_{22}H_{18}ClN_5O_2S_2$	484,00

1377		$C_{22}H_{20}ClN_5O2$	421,88
1378		$C_{22}H_{20}ClN_5O_2$	421,88

Scheme 1 A synthetic scheme of the C(6)-ester template.

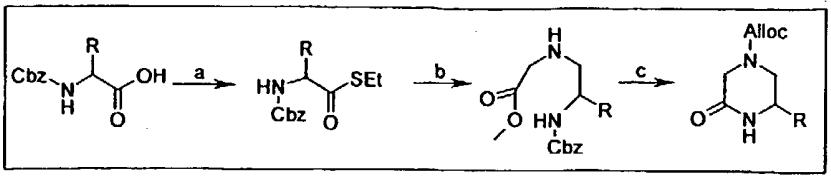


Reagents: (a) 1. PIFA, Py; 2. $SOCl_2$, MeOH; 3. $BrCH_2CO_2Me$. (b) 1. Pd on C, H_2; 2. Alloc-Cl, Et_3N.

Example 1379 (*R*)-5-Oxo-piperazine-1,3-dicarboxylic acid 1-allyl ester 3-methyl ester.

To a solution containing methyl (*R*)-6-oxopiperazine-2-carboxylate (1.32 g, 8.35 mmol), prepared by the method of Aebischer, in anhydrous dichloromethane (30 mL) at 0 °C was added triethylamine (1.26 g, 12.5 mmol) followed by allylchloroformate (1.20 g, 10.0 mmol). After 1 h, the reaction mixture was poured onto a 1:1 mixture of CH_2Cl_2/water (200 mL), acidified using 1N HCl and the layers were separated. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was chromatographed on silica gel (CH_2Cl_2 to 1% MeOH/CH_2Cl_2) to provide 1.22 g (60%) of (*R*)-5-oxo-piperazine-1,3-dicarboxylic acid 1-allyl ester 3-methyl ester as a viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.43 (bs, 1H), 5.90 (m, 1H), 5.26 (m, 2H), 4.61 (m, 2H), 4.05-4.26 (m, 3H), 3.80 (s, 3H), 3.72 (m, 2H) ppm. Mass Spectrum: (ISP loop) *m/z* 243 (M+H).

Scheme 2 A synthetic scheme of the C(6)-alkyl templates.



Reagents: (a). DCC, EtSH, CH_2Cl_2. (b). 1. TES, Pd/C, Acetone. 2. H_2N-Gly-OMe*HCl, $NaBH_3(CN)$, MeOH. (c). 1. Pd/C, MeOH, H_2. 2. Alloc-Cl, Et_3N, CH_2Cl_2.

Example 890: (*R*)-3-Isopropyl-5-oxo-piperazine-1-carboxylic acid allyl ester.

A. (*R*)-2-Benzyloxycarbonylamino-3-methyl-thiobutyric acid S-ethyl ester. To a solution containing (*R*)-2-benzyloxycarbonylamino-3-methyl-butyric acid (5.0 g, 20.0 mmol) in anhydrous CH_2Cl_2 (20 mL) was added DMAP (258 mg, 2.0 mmol) followed by chilled EtSH (1.6 mL, 22.0 mmol). Dicyclohexylcarbodiimide (4.5 g, 22.0 mmol) was added in one portion and the reaction was complete after 30 min. The solid material was removed by vacuum filtration and the filtrate was concentrated. The crude product was purified by flash silica gel chromatography (hexane to 8:1 hexane/EtOAc) to provide (*R*)-2-benzyloxycarbonylamino-3-methyl-thiobutyric acid S-ethyl ester (5.21 g, 88%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 1.23 (t, *J* = 7.5 Hz, 3H), 2.27 (m, 1H), 2.88 (q, *J* = 7.5 Hz, 2H), 4.35 (dd, *J* = 9.5, 4.6 Hz, 1H), 5.13 (s, 2H), 5.25 (br d, *J* = 9.5 Hz, 1H), 7.30-7.36 (m, 5H) ppm.

Using the appropriate amino acids the following compounds were prepared:

Example	Name	m/z(M+H)$^+$
1380	(*S*)-2-Benzyloxycarbonylamino-3-methyl-thiobutyric acid S-ethyl ester.	296
1381	(*R*)-2-Benzyloxycarbonylamino-4-methyl-pentanethioic acid S-ethyl ester.	310
1382	(*S*)-2-Benzyloxycarbonylamino-4-methyl-pentanethioic acid S-ethyl ester.	310
1383	(*S*)-2-Benzyloxycarbonylamino-thiopropionic acid S-ethyl ester.	268
1384	(*R*)- 2-Benzyloxycarbonylamino-3-methoxy-thiopropionic acid S-ethyl ester	298

1385	(*S*)- 2-Benzyloxycarbonylamino-3-methoxy-thiopropionic acid S-ethyl ester	298
1386	(*S*)-3-Benzyloxycarbonylamino-3-ethylsulfanylcarbonyl-propionic acid tert-butyl ester	368

B. (*R*)-(1-Formyl-2-methyl-propyl)-carbamic acid benzyl ester. To a solution containing (*R*)-2-benzyloxycarbonylamino-3-methyl-thiobutyric acid S-ethyl ester (5.2 g, 17.6 mmol) in acetone (100 mL) was added Pd-on-C (10%, 233 mg). The heterogeneous mixture was cooled to 0 °C and Et_3SiH (8.4 mL, 53 mmol) was quickly added. After 30 min, the reaction mixture was filtered through a pad of celite and the filtrate concentrated and partitioned between hexane (200 mL) and acetonitrile (300 mL). The layers were separated and the ACN phase was washed once with hexane (100 mL) and then concentrated to afford crude (*R*)-(1-formyl-2-methyl-propyl)-carbamic acid benzyl ester (4.13 g) which was used directly without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30 (m, 1H), 4.31 (m, 1H), 5.09 (s, 2H), 5.45 (br, 1H), 7.30-7.45 (m, 5H), 9.65 (s, 1H) ppm.

C. (*R*)-(2-Benzyloxycarbonylamino-3-methyl-butylamino)-acetic acid ethyl ester. To a solution containing crude (*R*)-(1-formyl-2-methyl-propyl)-carbamic acid benzyl ester (4.13 g, 17.6 mmol) in anhydrous MeOH (100 mL) at 0 °C was added glycine ethyl ester hydrochloride (9.5 g, 70.4 mmol). After 10 min, 1.0 M $NaCNBH_3$ in THF (27 mL, 27 mmol) was added and the heterogeneous reaction mixture was allowed to warm to ambient temperature overnight. The reaction mixture was concentrated and the residue was partitioned between diethyl ether (200 mL) and saturated aqueous $NaHCO_3$ (200 mL). The layers were separated and the aqueous layer was extracted twice with diethyl ether (2 x 200 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to afford the crude product which was purified by flash silica gel chromatography (hexane/EtOAc, 2:1 to 1:1) which provided 4.2 g (74%) of (*R*)-(2-benzyloxycarbonylamino-3-methyl-butylamino)-acetic acid ethyl ester as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, J = 7.0 Hz, 3H), 0.92 (d, J = 7.0 Hz, 3H), 1.25 (t, J = 8.4 Hz, 3H), 1.62 (br s, 1H), 1.80 (m, 1H), 2.65-2.70 (m, 2H), 3.37 (ABq, Δ_{AB} = 32.3 Hz, J_{AB} = 17.4 Hz, 2H), 4.16 (q, J = 8.4 Hz, 2H), 5.14 (s, 2H), 7.28-7.36 (m, 5H) ppm. Mass Spectrum: (ion spray): *m/z* 323 (M+H).

The following examples were prepared according to the above procedure:

Example	Name	m/z(M+H)$^+$
1387	(*S*)-(2-Benzyloxycarbonylamino-3-methyl-butylamino)-acetic acid ethyl ester.	323
1388	(*S*)-(2-Benzyloxycarbonylamino-4-methyl-pentylamino)-acetic acid methyl ester.	323
1389	(*R*)-(2-Benzyloxycarbonylamino-4-methyl-pentylamino)-acetic acid methyl ester.	323
1390	(*S*)-(2-Benzyloxycarbonylamino-propylamino)-acetic acid methyl ester.	295
1391	(*R*)-(2-Benzyloxycarbonylamino-3-methoxy-propylamino)-acetic acid ethyl ester	325
1392	(*S*)-(2-Benzyloxycarbonylamino-3-methoxy-propylamino)-acetic acid ethyl ester	325
1393	(*S*)-3-Benzyloxycarbonylamino-4-(methoxycarbonylmethyl-amino)-butyric acid tert-butyl ester.	395

D. (*R*)-6-Isopropyl-piperazin-2-one. To a Parr vessel charged with (*R*)-(2-benzyloxycarbonylamino-3-methyl-butylamino)-acetic acid ethyl ester (4.2 g, 13.0 mmol) in MeOH (130 mL) was added Pd-on-C (10%, 396 mmol). The reaction vessel was pressurized with 40 PSI hydrogen pressure and shaken for 4 h at ambient temperature. The reaction mixture was then filtered through celite and the filtrate concentrated to provide 1.77 g (95%) of (*R*)-6-isopropyl-piperazin-2-one as an off-white solid which was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 1.68 (sept, *J* = 6.7 Hz, 1H), 2.67 (dd, *J* = 12.8, 8.9 Hz, 1H), 3.09-3.22 (m, 2H), 3.46 (ABq, Δ_{AB} = 34.3 Hz, J_{AB} = 17.5 Hz, 2H), 5.97 (br s, 1H) ppm.

The following examples were prepared according to the above procedure:

Example	Name	m/z(M+H)$^+$
1394	(*S*)-6-Isopropyl-piperazine-2-one.	142
1395	(*S*)-6-Isobutyl-piperazine-2-one.	157
1396	(*R*)-6-Isobutyl-piperazine-2-one.	157
1397	(*S*)-6-Methyl-piperazine-2-one.	
1398	(*R*)-6-Methoxymethyl-piperazin-2-one	144
1399	(*S*)-6-Methoxymethyl-piperazin-2-one	144

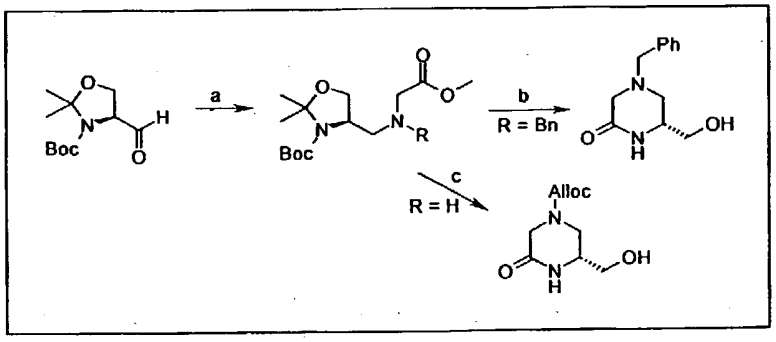
E. (*R*)-3-Isopropyl-5-oxo-piperazine-1-carboxylic acid allyl ester.

To a solution of (*R*)-6-isopropyl-piperazin-2-one (1.77 g, 12.5 mmol) in anhydrous CH_2Cl_2 (45 mL) at 0 °C was added triethylamine (2.6 mL, 18.7 mmol) followed by allyl chloroformate (1.6 mL, 15.0 mmol). The mixture was stirred at 0 °C for 30 min and at ambient temperature for 30 min then was partitioned between CH_2Cl_2 (30 mL) and water (75 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 75 mL) and the combined organic phases were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated on to silica gel. The mixture was purified by flash silica gel chromatography (CH_2Cl_2→1% MeOH/CH_2Cl_2 →2%→4%) to provide 2.62 g (93%) of (*R*)-3-isopropyl-5-oxo-piperazine-1-carboxylic acid allyl ester as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) d 6.85-7.08 (m, 1H), 5.82-5.99 (m, 1H), 5.19-5.33 (m, 2H), 4.60 (d,*J* = 5.6 Hz, 2H), 4.21 (d, *J* = 18.4 Hz, 1H), 3.97 (d, *J* = 18.4 Hz, 1H), 3.71-3.90 (m, 1H), 3.16-3.37 (m, 2H), 1.69-1.81 (m, 1H), 0.94-1.01 (m, 6H) ppm. Mass Spectrum: (ESI) *m/z* 226 $(M+H)^+$.

The following examples were prepared according to the above procedure:

Example	Name	m/z(M+H)$^+$
1400	(*S*)-3-Isopropyl-5-oxo-piperazine-1-carboxylic acid allyl ester.	226
1401	(*S*)-3-Isobutyl-5-oxo-piperazine-1-carboxylic acid allyl ester.	241
1402	(*R*)-3-Isobutyl-5-oxo-piperazine-1-carboxylic acid allyl ester.	241
1403	(*S*)-3-Methyl-5-oxo-piperazine-1-carboxylic acid allyl ester.	199
1404	(*R*)-3-Methoxymethyl-5-oxo-piperazine-1-carboxylic acid allyl ester	229
1405	(*S*)-3-Methoxymethyl-5-oxo-piperazine-1-carboxylic acid allyl ester	229
1406	(*S*)-3-tert-Butoxycarbonylmethyl-5-oxo-piperazine-1-carboxylic acid allyl ester	298

Scheme 3 A synthetic scheme of the *C*(6)-Hydroxymethylketopiperazine.



Reagents: (a) 1. $RNHCH_2CO_2Me$, $NaB(OAc)_3H$, 4A MS. (b) Sat'd HCl / MeOH; K_2CO_3. (c) 1. Alloc-Cl, Et_3N, CH_2Cl_2. 2. Sat'd HCl / MeOH; K_2CO_3.

Example 1407 (*R*)-4-Benzyl-6-hydroxymethyl-piperazin-2-one

A: (*R*)-4-[(Benzyl-ethoxycarbonylmethyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester. To a mixture of the Garner's aldehyde 1 (Garner, P., Park, J. -M. Org. Synthesis 1991, 70, 18) (31 g, 135 mmol), *N*-benzyl glycine ethyl ester (28.7 g, 149 mmol) and powdered 4Å MS (40 g) in 1,2-dichloroethane (300 mL) was added sodium triacetoxy-borohydride (43 g, 203 mmol) at 0 °C. After 12 h at ambient temperature, the reaction mixture was quenched with saturated $NaHCO_3$ solution, filtered through Celite, and extracted with CH_2Cl_2. The extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated. Chromatography on SiO_2 (hexanes/EtOAc, 10 : 1 to 3 : 1) provided 42.6 g (78%) of (*R*)-4-[(benzyl-ethoxycarbonylmethyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester as an oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.32-7.21 (m, 5H), 4.14 (q, *J* = 6.9 Hz, 2H), 4.1-3.9 (m, 3H), 3.85-3.7 (m, 2H), 3.41-3.24 (m, 2H), 3.0 (d, *J* = 12.5 Hz, 1H), 2.68-2.55 (m, 1H), 1.57 (m, 3H), 1.47 (s, 9H), 1.45 (m, 3H), 1.26 (t, *J* = 7.1 Hz, 3H) ppm. Mass Spectrum: (ESI) *m/z* 407 $(M+H)^+$.

B: (*R*)-4-Benzyl-6-hydroxymethyl-piperazin-2-one. A solution of (*R*)-4-[(benzyl-ethoxycarbonylmethyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (42.6 g, 105 mmol) in MeOH (500 mL) was bubbled with anhydrous HCl gas for 30 min at 0°C. After 15 h at ambient temperature, the mixture was concentrated under reduced pressure and treated with K_2CO_3 (100 g, 0.72 mol) in MeOH (500 mL). Stirring was continued until the pH of the aliquot was basic (~24 h) after which the suspension turned colorless. The mixture was filtered, and the filtrate was concentrated and chromatographed on SiO_2 (5% to 15% MeOH in CH_2Cl_2) to afford 23 g (100%) of (*R*)-4-benzyl-6-hydroxymethyl-piperazin-2-one as a solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.28 (m, 5H), 6.95 (s, 1H), 3.68-3.6 (m, 2H), 3.58-3.45 (m, 4H), 3.17 (d, *J* = 14 Hz, 1H), 3.11 (d, *J* = 14 Hz, 1H), 2.71 (dd, *J* = 10.0, 3.5 Hz, 1H), 2.56 (dd, *J* = 9.5, 4.5 Hz, 1H) ppm. Mass Spectrum: (ESI) *m/z* 221 $(M+H)^+$.

Example 1408 (*R*)-3-Hydroxymethyl-5-oxo-piperazine-1-carboxylic acid allyl ester

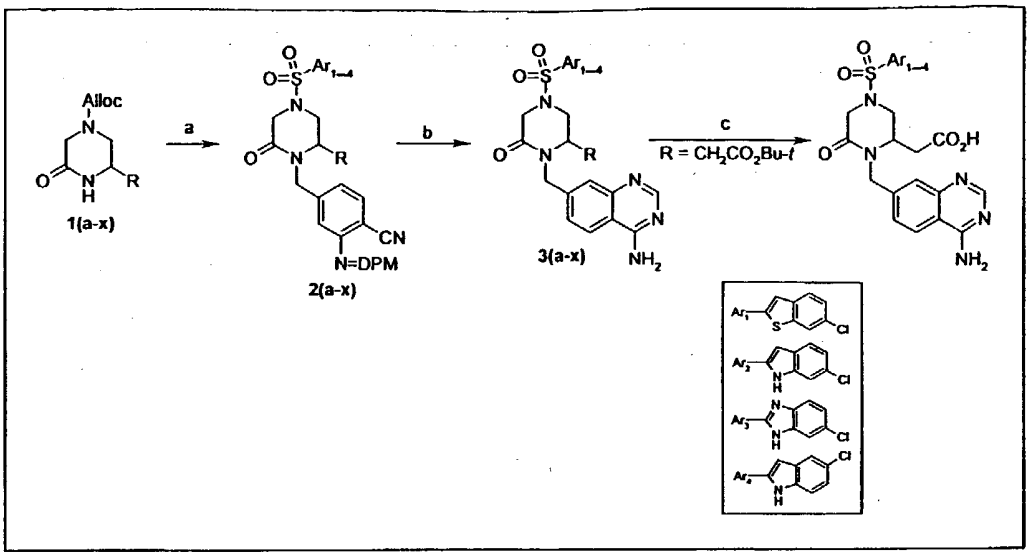
A: (*R*)-4-[(Ethoxycarbonylmethyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester A solution of glycine methyl ester hydrochloride (26 g, 208 mmol) and Et_3N (28 mL, 203 mmol) in MeOH (200 mL) at 0 °C was treated with the Garner's aldehyde 1 (12 g, 52 mmol), followed by addition of a 1.0 M solution of $NaBH_3CN$ in THF (60 ml, 60 mmol.). After 3 hours at ambient temperature, the reaction mixture was concentrated and diluted with EtOAc and sat $NaHCO_3$ solution. The organic phase was separated, dried ($MgSO_4$), filtered, and

concentrated. Chromatography on SiO_2 (hexanes/EtOAc, 2 : 1 to 1 : 2) provided 14.5 g (92%) of (*R*)-4-[(ethoxycarbonylmethyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95 (s, 2H). 3.75 (m, 1H), 3.7 (s, 3H), 3.45 (s, 2H), 2.7 (m, 2H), 1.5 (m, 15H) ppm. Mass Spectrum: (ESI) *m/z* 303 $(M+H)^+$.

B. (*R*)-3-Hydroxymethyl-5-oxo-piperazine-1-carboxylic acid allyl ester. To a solution of (*R*)-4-[(ethoxycarbonylmethyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (14.5 g, 48 mmol) in CH_2Cl_2 (200 mL) at 0 °C was added triethylamine (12 mL, 86 mmol) followed by allylchloroformate (6.6 mL, 63 mmol). After 1 h at ambient temperature, the reaction mixture was diluted with saturated NH_4Cl and extracted with CH_2Cl_2. The extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude residue was chromatographed on SiO_2 (hexanes/EtOAc, 4:1) to provide 15.4 g (83%) of (*R*)-4-[(allyloxycarbonyl-ethoxycarbonylmethyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester as a viscous oil. Mass Spectrum: (ESI) *m/z* 387 $(M+H)^+$.

A solution of (*R*)-4-[(allyloxycarbonyl-ethoxycarbonylmethyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (15.4 g, 40 mmol) in CH_2Cl_2 (20 mL) and TFA (150 mL) was stirred for 12 h at ambient temperature. The mixture was concentrated under reduced pressure (azeotrophic evaporation with toluene) and treated with excess K_2CO_3 in MeOH (300 mL). Stirring was continued until the pH of the aliquot was basic (~24 h). The mixture was filtered, and the filtrate was concentrated and chromatographed on SiO_2 (5% to 20% MeOH in CH_2Cl_2) to afford 6 g (70%) of (*R*)-3-hydroxymethyl-5-oxo-piperazine-1-carboxylic acid allyl ester as a solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 (s, 1H), 5.97-5.88 (m, 1H), 5.35-5.24 (m, 2H), 4.62 (d, J = 5.7 Hz, 2H), 4.2-4.1 (m, 2H), 3.8-3.4 (m, 5H), 2.65 (s, 1H) ppm. Mass Spectrum: (ESI) *m/z* 214 $(M+H)^+$.

Scheme 4 A synthetic scheme of the C(6)-substituted sulfonamide inhibitors.



Reagents: (a). 1. NaH, 4-bromomethyl-2-diphenylmethyleneaminobenzonitrile, THF. 2. $Pd(PPh_3)_4$, morpholine, CH_2Cl_2, 3. sulfonyl chloride, Et_3N, CH_2Cl_2, (b). 1. c-HCl , MeOH; 2. Triazine, AcOH, EtOH, reflux. (c). TFA, CH_2Cl_2.

Example 1409 (*R*)-1-(4-Amino-quinazolin-7-yl-methyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isopropyl-piperazin-2-one.

A. (*R*)-4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-isopropyl-5-oxo-piperazine-1-carboxylic acid allyl ester. To a solution of (*R*)-3-isopropyl-5-oxo-piperazine-1-carboxylic acid allyl ester (2.60 g, 11.5 mmol) in anhydrous THF (30 mL) and anhydrous DMF (2 mL) at 0 °C was added sodium hydride (600 mg, 60% dispersion in mineral oil, 14.95 mmol). The mixture was stirred at 0 °C for 15 min until gas evolution ceased, then 2-(benzyhydrylidene-amino)-4-bromomethyl-benzonitrile (4.41 g, 12.1 mmol) was added. The reaction was allowed to warm slowly to ambient temperature over 3 h and the now black solution was quenched with saturated aqueous NH_4Cl (100 mL) and partitioned between water (250 mL) and Et_2O (250 mL). The aqueous layer was extracted with Et_2O (2 x 250 mL) and the combined organic phases were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash silica gel chromatography (CH_2Cl_2→1%MeOH/CH_2Cl_2→1.8%→2%) to afford 4.98 g (83%) of (*R*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-isopropyl-5-oxo-piperazine-1-carboxylic acid allyl ester as a sticky brown solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.2 Hz, 2H), 7.17-7.52 (m, 10H), 6.86 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.58 (s, 1H), 5.83-5.98 (m, 1H), 5.18-5.42 (m, 3H), 4.61 (d, *J* = 5.5 Hz, 2H), 4.20-4.31 (m, 1H), 3.92-4.16 (m, 2H),

3.71 (d, J = 15.1 Hz, 1H), 2.70-2.78 (m, 2H), 1.87-2.02 (m, 1H), 0.94 (d,J = 6.8 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H) ppm. Mass Spectrum: (ESI) *m/z* 521 $(M+H)^+$.

B (*R*)-2-(Benzhydrylidene-amino)-4-(2-isopropyl-6-oxo-piperazin-1-ylmethyl)-benzonitrile. To a solution of (*R*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-isopropyl-5-oxo-piperazine-1-carboxylic acid allyl ester (2.0 g, 3.85 mmol) in anhydrous CH_2Cl_2 (40 mL) at ambient temperature was added morpholine (1.6 mL, 19.2 mmol) followed by *tetrakis* (triphenyl phosphine) palladium (444 mg, 0.385 mmol). The yellow solution was stirred for 1 h then concentrated on to silica gel and flash column chromatographed (CH_2Cl_2→1%MeOH/CH_2Cl_2 →2%) to provide 1.4 g (83%) of (*R*)-2-(benzhydrylidene-amino)-4-(2-isopropyl-6-oxo-piperazin-1-ylmethyl)-benzonitrile as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 7.2 Hz, 2H), 7.19-7.69 (m, 9H), 6.86 (dd, J = 7.9, 1.4 Hz, 1H), 6.60 (d, J = 1.0 Hz, 1H), 5.31 (d, J = 15.4 Hz, 1H), 3.85 (d, J = 15.5 Hz, 1H), 3.72 (t, J = 4.6 Hz, 1H), 3.43-3.59 (m, 1H), 2.82-2.91 (m, 2H), 2.42-2.48 (m,1H), 1.96-2.05 (m, 1H), 0.86 (d, J = 7.0 Hz, 3H), 0.82 (d, J = 7.0 Hz, 3H) ppm. Mass Spectrum: (ESI) *m/z* 437 $(M+H)^+$.

C (*R*)-2-(Benzhydrylidene-amino-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-isopropyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile. To a solution of (*R*)-2-(benzhydrylidene-amino)-4-(2-isopropyl-6-oxo-piperazin-1-ylmethyl)-benzonitrile (0.61 g, 1.4 mmol) in anhydrous CH_2Cl_2 (15 mL) at 0 °C was added diisopropylethylamine (320 μL, 1.82 mmol) followed by 6-chloro-benzo[b]thiophene-2-sulfonyl chloride (375 mg, 1.4 mmol). The reaction was stirred at ambient temperature for 1 h then concentrated on to silica gel and flash column chromatographed (Hexane:EtOAc, 4:1→2:1) to provide 681 mg (73%) of (*R*)-2-(benzyhdrylidene-amino)-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-isopropyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile as a yellow gum. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78-7.86 (m, 3H), 7.72 (d, J = 7.0 Hz, 2H), 7.32-7.52 (m, 5H), 7.09-7.27 (m, 5H), 6.77 (dd,J = 7.9, 1.4 Hz, 1H), 6.53 (d, J = 1.1 Hz, 1H), 5.30 (d, J = 15.2 Hz, 1H), 4.03-4.16 (m, 1H), 3.75 (d,J = 15.2 Hz, 1H), 3.57 (d, J = 16.7 Hz, 1H), 2.82-2.90 (m, 1H), 2.63 (dd, J = 12.3, 3.7 Hz, 1H), 2.07-2.17 (m, 1H), 0.93-1.04 (m, 6H) ppm. Mass Spectrum: (ESI) *m/z* 667 $(M+H)^+$.

Examples:

Example	Name	m/z$(M+H)^+$
1410	(*R*)-2-(Benzhydrylidene-amino)-4-[4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-2-isopropyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile	651
1411	(*R*)-2-{4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-isopropyl-5-	750

	oxo-piperazine-1-sulfonyl}-5-chloro-indole-1-carboxylic acid tert-butyl ester	
1412	(*R*)-2-{4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-isopropyl-5-oxo-piperazine-1-sulfonyl}-6-chloro-indole-1-carboxylic acid tert-butyl ester	750
1413	(*S*)-2-(benzyhdrylidene-amino)-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-isopropyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile	667
1414	(*S*)-2-(Benzhydrylidene-amino)-4-[4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-2-isopropyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile	651
1415	(*S*)-2-{4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-isopropyl-5-oxo-piperazine-1-sulfonyl}-5-chloro-indole-1-carboxylic acid tert-butyl ester	750
1416	(*S*)-2-{4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-isopropyl-5-oxo-piperazine-1-sulfonyl}-6-chloro-indole-1-carboxylic acid tert-butyl ester	750
1417	(*R*)-2-(benzyhdrylidene-amino)-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-isobutyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile	681
1418	(*R*)-2-(Benzhydrylidene-amino)-4-[4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-2-isobutyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile	665
1419	(*R*)-2-{4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-isobutyl-5-oxo-piperazine-1-sulfonyl}-5-chloro-indole-1-carboxylic acid tert-butyl ester	764
1420	(*R*)-2-{4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-isobutyl-5-oxo-piperazine-1-sulfonyl}-6-chloro-indole-1-carboxylic acid tert-butyl ester	764
1421	(*S*)-2-(benzyhdrylidene-amino)-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-isobutyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile	681
1422	(*S*)-2-(Benzhydrylidene-amino)-4-[4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-2-isobutyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile	665
1423	(*S*)-2-{4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-isobutyl-5-oxo-piperazine-1-sulfonyl}-5-chloro-indole-1-carboxylic acid tert-butyl ester	764
1424	(*S*)-2-{4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-isobutyl-5-oxo-piperazine-1-sulfonyl}-6-chloro-indole-1-carboxylic acid tert-butyl	764

	ester	
1425	(*S*)-2-(benzyhdrylidene-amino)-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-methyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile	
1426	(*S*)-2-(Benzhydrylidene-amino)-4-[4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-2-methyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile	
1427	(*S*)-2-{4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-methyl-5-oxo-piperazine-1-sulfonyl}-5-chloro-indole-1-carboxylic acid tert-butyl ester	
1428	(*S*)-2-{4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-methyl-5-oxo-piperazine-1-sulfonyl}-6-chloro-indole-1-carboxylic acid tert-butyl ester	
1429	(*R*)-2-(Benzhydrylidene-amino)-4-[4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile	653
1430	(*S*)-2-(Benzhydrylidene-amino)-4-[4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile	653
1431	(*R*)-2-{4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-methoxymethyl-5-oxo-piperazine-1-sulfonyl}-6-chloro-indole-1-carboxylic acid tert-butyl ester	752
1432	(*S*)-2-{4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-methoxymethyl-5-oxo-piperazine-1-sulfonyl}-6-chloro-indole-1-carboxylic acid tert-butyl ester	752
1433	(*S*)-2-{4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-methoxymethyl-5-oxo-piperazine-1-sulfonyl}-5-chloro-indole-1-carboxylic acid tert-butyl ester	752
1434	(*S*)-[1-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-yl]-acetic acid tert-butyl ester	739

Example 1435 (*R*)-2-Amino-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-isopropyl-6-oxo-piperazin-1-ylmethyl]benzonitrile. To a solution of (*R*)-2-(benzyhdrylidene-amino)-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-isopropyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile (681 mg, 1.02 mmol) in MeOH (15 mL) and THF (3 mL) at 0 °C was added concentrated HCl (10 drops). The solution was stirred at 0 °C for 15 min then concentrated to dryness and the residue purified by flash silica gel chromatography (CH_2Cl_2→1%MeOH/CH_2Cl_2→2%) to provide 481 mg (94%) of (*R*)-2-amino-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-isopropyl-6-oxo-piperazin-1-ylmethyl]benzonitrile as a crunchy white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78-

7.88 (m, 3H), 7.46 (dd, J = 8.6, 1.8 Hz, 1H), 7.23-7.30 (m, 1H), 6.55 (s, 1H), 6.49 (dd, J = 7.9, 1.4 Hz, 1H), 5.30 (d, J = 15.3 Hz, 1H), 4.37 (s, 2H), 4.08-4.22 (m, 1H), 3.78-3.90 (m, 2H), 3.57-3.69 (m, 1H), 3.10-3.18 (m, 1H), 2.78 (dd, J = 12.5, 4.0 Hz, 1H), 2.18-2.29 (m, 1H), 1.08 (d, J = 6.9 Hz, 3H), 1.04 (d, J = 6.9 Hz, 3H) ppm. Mass Spectrum: (ESI) *m/z* 503 $(M+H)^+$.

Example 1436: (*R*)-1-(4-Amino-quinazolin-7-yl-methyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isopropyl-piperazin-2-one. To a suspension of (*R*)-2-amino-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-isopropyl-6-oxo-piperazin-1-ylmethyl]benzonitrile (468 mg, 0.93 mmol) in abs. EtOH (12 mL) was added glacial acetic acid (540 μL, 9.31 mmol) and triazine (775 mg, 9.31 mmol). The mixture was warmed to reflux (became homogeneous) stirred for 16 h, cooled and concentrated to dryness. The crude product was purified by reverse phase HPLC on a 2" Dynamax C18 column (10→100% ACN in H_2O/0.1% TFA) to provide 365 mg (61%) of (*R*)-1-(4-amino-quinazolin-7-yl-methyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isopropyl-piperazin-2-one as a white, lyophilized solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.70 (br s, 2H), 8.75 (s, 1H), 8.24-8.34 (m, 2H), 8.19 (s, 1H), 8.06 (d, J = 8.7 Hz, 1H), 7.53-7.62 (m, 3H), 5.07 (d, J = 16.4 Hz, 1H), 4.45 (d, J = 16.3 Hz, 1H), 4.06 (d, J = 16.4 Hz, 1H), 3.83 (d, J = 16.2 Hz, 1H), 3.63 (d, J = 16.2 Hz, 1H), 3.34-3.45 (m, 1H), 3.02 (AB quartet, J = 12.6, 3.6 Hz, 1H), 2.11-2.22 (m, 1H), 0.99 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H) ppm. Mass Spectrum: (ESI): *m/z* 530 $(M+H)^+$.

The following examples were prepared according to the above procedure:

Example 1437 (*R*)-1-(4-Aminoquinazolin-7-yl-methyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isopropyl-piperazin-2-one.

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.70 (bs, 2H); 8.76 (s, 1H); 8.29 (d, J = 8.6 Hz, 1H); 7.65-7.73 (m, 2H); 7.55-7.62 (m, 2H); 7.40 (d, J = 8.7 Hz, 1H); 5.05 (d, J = 16.2 Hz, 1H); 4.47 (d, J = 16.2 Hz, 1H); 4.13 (d, J = 16.6 Hz, 1H); 3.80-3.93 (m, 2H); 3.35-3.65 (m, 1H); 3.18 (AB q, J = 12.9, 3.6 Hz, 1H), 2.09-2.19 (m, 1H); 0.99 (d, J = 6.8 Hz, 3H); 0.93 (d, J = 6.9 Hz, 3H) ppm. Mass Spectrum: (ESI) *m/z* 514 $(M+H)^+$.

Example 1438 (*S*)-1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isopropyl-piperazin-2-one.

^{1}H NMR (300 MHz, d_6-DMSO) ↗ 0.96 (dd, J = 15.9, 6.85 Hz, 6H), 2.19 (m, 1H), 3.02 (dd, J = 12.4, 3.6 Hz, 1H), 3.40 (m, 2H), 3.82 (d, J = 12.4 Hz, 1H), 4.03 (d, J = 16.3 Hz, 1H), 4.47 (d, J = 16.3 Hz, 1H), 5.06 (d, J = 16.3 Hz, 1H), 7.55 (m, 3H), 8.06 (d, J = 8.6 Hz, 1H), 8.20 (s, 1H), 8.28

(d, J = 8.6 Hz, 1H), 8.33 (d, J = 1.9 Hz, 1H), 8.76 (s, 1H), 9.71 (br.s, 2H) ppm. Mass Spectrum: (ESI) *m/z* 530 $(M+H)^+$.

Example 1439 (*S*)-1-(4-Aminoquinazolin-7-yl-methyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isopropyl-piperazin-2-one.

^{1}H NMR (300 MHz, d_6-DMSO) ↗ 0.96 (dd, J = 17.84, 6.86 Hz, 6H), 2.15 (m, 1H), 3.18 (dd, J = 12.8, 3.5 Hz, 2H), 3.88 (m, 3H), 4.13 (d, J = 16.5 Hz, 1H), 4.47 (d, J = 16.3 Hz, 1H), 5.06 (d, J = 16.3 Hz, 1H), 7.40 (dd, J = 8.7, 1.8 Hz, 1H), 7.57 (s, 1H), 7.60 (d, J = 8.65 Hz, 1H), 7.74 (m, 2H), 8.29 (d, J = 8.54 Hz, 1H), 8.76 (s, 1H), 9.71 (br. s, 2H) ppm. Mass Spectrum: (ESI)*m/z* 514 $(M+H)^+$.

Example 1440 (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chlorobenzo[b]thiophene-2-sulfonyl)-6-isobutyl-piperazin-2-one.

^{1}H NMR (300 MHz, d_6-DMSO) ↗ 0.82 (dd, J = 17.6, 6.4 Hz, 6H), 1.41 (m, 1H), 1.60 (m, 1H), 1.74 (m, 1H), 3.06 (d, J = 10.0 Hz, 1H), 3.42 (d, J = 8.8 Hz, 1H), 3.65 (d, J = 16.2 Hz, 1H), 3.73 (s, 1H), 4.05 (d, J = 16.2 Hz, 1H), 4.41 (d, J = 16.6 Hz, 1H), 5.02 (d, J = 16.6 Hz, 1H), 7.53 (s, 1H), 7.58 (dd, J = 8.6, 2.0 Hz, 2H), 8.06 (d, J = 8.6 Hz, 1H), 8.22 (s, 1H), 8.29 (d, J = 8.6 Hz, 1H), 8.33 (d, J = 1.8 Hz, 1H), 8.77 (s, 1H), 9.74 (s, 2H) ppm. Mass Spectrum: (ESI)*m/z* 544 $(M+H)^+$.

Example 1441 (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isobutyl-piperazin-2-one.

^{1}H NMR (500 MHz, d_6-DMSO) ↗ 0.82 (dd, J = 24.0, 6.6 Hz, 6H), 1.40 (m, 1H), 1.60 (m, 1H), 1.69 (m, 1H), 3.33 (d, J = 10.2 Hz, 1H), 3.43 (m, 1H), 3.80 (d, J = 12.7 Hz, 1H), 3.89 (s, 1H), 3.93 (d, J = 9.8 Hz, 1H), 4.18 (d, J = 16.1 Hz, 1H), 4.42 (d, J = 16.6 Hz, 1H), 5.04 (d, J = 16.6 Hz, 1H), 7.41 (dd, J = 8.8, 2.0 Hz, 1H), 7.56 (s, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.73 (d, J = 8.8 Hz, 1H), 7.79 (d, J = 2.0 Hz, 1H), 8.33 (d, J = 8.3 Hz, 1H), 8.80 (s, 1H), 9.78 (s, 1H) ppm. Mass Spectrum: (ESI) *m/z* 544 $(M+H)^+$.

Example 1442 (*S*)-1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isobutyl-piperazin-2-one.

^{1}H NMR (300 MHz, d_6-DMSO) ↗ 0.82 (dd, J = 17.6, 6.4 Hz, 6H), 1.41 (m, 1H), 1.74 (m, 1H), 3.06 (d, J = 10.0 Hz, 1H), 3.42 (d, J = 8.8 Hz, 1H), 3.65 (d, J = 16.2 Hz, 1H), 3.73 (s, 1H), 4.05 (d, J = 16.2 Hz, 1H), 4.41 (d, J = 16.6 Hz, 1H), 5.02 (d, J = 16.6 Hz, 1H), 7.53 (s, 1H), 7.58 (dd,

J = 8.6, 2.0 Hz, 2H), 8.06 (d, J = 8.6 Hz, 1H), 8.22 (s, 1H), 8.29 (d, J = 8.6 Hz, 1H), 8.33 (d, J = 1.8 Hz, 1H), 8.77 (s, 1H), 9.74 (s, 2H) ppm. Mass Spectrum: (ESI) *m/z* 544 $(M+H)^+$.

Example 1443 (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isobutyl-piperazin-2-one.

^{1}H NMR (500 MHz, d_6-DMSO) ↗ 0.82 (dd, J = 24.0, 16.6 Hz, 6H), 1.40 (m, 1H), 1.60 (m, 1H), 1.69 (m, 1H), 3.33 (d, J = 10.2 Hz, 1H), 3.43 (m, 1H), 3.80 (d, J = 12.7 Hz, 1H), 3.89 (s, 1H), 3.93 (d, J = 9.8 Hz, 1H), 4.18 (d, J = 16.1 Hz, 1H), 4.42 (d, J = 16.6 Hz, 1H), 5.04 (d, J = 16.6 Hz, 1H), 7.41 (dd, J = 8.8, 2.0 Hz, 1H), 7.56 (s, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.73 (d, J = 8.8 Hz, 1H), 7.79 (d, J = 2.0 Hz, 1H), 8.33 (d, J = 8.3 Hz, 1H), 8.80 (s, 1H), 9.78 (s, 1H) ppm. Mass Spectrum: (ESI) *m/z* 528 $(M+H)^+$.

Example 1444 (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isobutyl-piperazin-2-one.

^{1}H NMR (500 MHz, d_6-DMSO) ↗ 0.82 (dd, J = 24.0, 6.6 Hz, 6H), 1.40 (m, 1H), 1.60 (m, 1H), 1.69 (m, 1H), 3.33 (d, J = 10.2 Hz, 1H), 3.43 (m, 1H), 3.80 (d, J = 12.7 Hz, 1H), 3.89 (s, 1H), 3.93 (d, J = 9.8 Hz, 1H), 4.18 (d, J = 16.1 Hz, 1H), 4.42 (d, J = 16.6 Hz, 1H), 5.04 (d, J = 16.6 Hz, 1H), 7.41 (dd, J = 8.8, 2.0 Hz, 1H), 7.56 (s, 1H), 7.73 (d, J = 8.8 Hz, 1H), 7.79 (d, J =2.0 Hz, 1H), 8.62 (s, 1H), 8.80 (s, 1H), 9.78 (s, 1H) ppm. Mass Spectrum: (ESI) *m/z* 562 $(M+H)^+$.

Example 1445 (*S*)-1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methyl-piperazin-2-one.

^{1}H NMR (300 MHz, DMSO-d_6) ↗ 8.37 (d, J = 10.2 Hz, 2H), 8.19 (s, 1H), 8.10 (d, J = 8.7 Hz, 1H), 7.73 (br. s, 2H), 7.60 (d, J = 8.6 Hz, 1H), 7.50 (s, 1H), 7.31 (d, J = 8.6 Hz, 1H), 5.06 (d, J = 15.8 Hz, 1H), 4.35 (d, J = 15.8 Hz, 1H), 3.98 (d, J = 16.0 Hz, 1H), 3.77 (d, J = 16.0 Hz, 1H), 3.62-3.48 (m, 2H), 3.21 (d, J = 9.2 Hz, 1H), 1.25 (d, J = 6.1 Hz, 3H) ppm. Mass Spectrum: (ESI) *m/z* 502 $(M+H)^+$.

Example 1446
(*S*)-1-(4-Aminoquinazolin-7-yl-methyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-methyl-piperazin-2-one.

^{1}H NMR (300 MHz, DMSO-d_6) ↗ 9.80 (d, J = 6.2 Hz, 2H), 8.82 (s, 1H), 8.35 (d, J = 8.6 Hz, 1H), 7.84 (s, 1H), 7.78 (d, J = 8.7 Hz, 1H), 7.64 (d, J = 8.7 Hz, 1H), 7.60 (s, 1H), 7.47 (d, J = 8.7 Hz,

1H), 4.98 (d, J = 16.5 Hz, 1H), 4.60 (d, J = 16.5 Hz, 1H), 4.19 (d, J = 16.4 Hz, 1H), 3.96 (d, J = 16.4 Hz, 1H), 3.60 (m, 3H), 1.26 (d, J = 6.1 Hz, 3H) ppm. Mass Spectrum: (ESI) *m/z* 486 $(M+H)^+$.

Example 1447 (*S*)-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-yl]-acetic acid tert-butyl ester

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.86-7.88 (m, 1H), 7.84 (d, J = 8.7 Hz, 1H), 7.80 (d, J = 0.55 Hz, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.59 (d, J = 1.2 Hz, 1H), 7.46 (dd, J = 8.6, 1.8 Hz, 1H), 7.33 (dd, J = 8.5, 1.6 Hz, 1H), 5.36 (d, J = 15.7 Hz, 1H), 4.24 (d, J = 17.1 Hz, 1H), 4.11 (d, J = 15.7 Hz, 1H), 3.95 (d, J = 12.4 Hz, 1H), 3.80-3.88 (m, 1H), 3.59 (d, J = 16.7 Hz, 1H), 2.86-2.98 (m, 2H), 2.65 (dd, J = 16.8, 2.5 Hz, 1H) 1.43 (s, 9H) ppm. Mass Spectrum: (ESI) *m/z* 602 $(M+H)^+$.

Example 1448 (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-piperazin-2-one

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.70 (s, 2H), 8.77 (s, 1H), 8.34 (d, J = 8.6 Hz, 1H), 8.28 (d, J = 8.6 Hz, 1H), 8.21 (s, 1H), 8.07 (d, J = 8.6 Hz, 1H), 7.54-7.62 (m, 2H), 7.50 (s, 1H), 4.95 (d, J = 16.5 Hz, 1H), 4.59 (d, J = 16.6 Hz, 1H), 4.02 (d, J = 16.5 Hz, 1H), 3.45-3.80 (m, 3H), 3.09-3.19 (m, 4H) ppm. Mass Spectrum: (ESI) *m/z* 532 $(M+H)^+$.

Example 1449 (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-piperazin-2-one

^{1}H NMR (300 MHz, DMSO-d_6) ↗ 8.44 (s, 1H), 8.36 (s, 1H), 8.21-8.09 (m, 5H), 7.58 (dd, J = 11.0, 1.3 Hz, 1H), 7.49 (s, 1H), 7.36 (d, J = 8.5 Hz, 1H), 5.06 (d, J = 16.0 Hz, 1H), 4.49 (d, J = 16.0 Hz, 1H), 4.04 (d, J = 16.1 Hz, 1H), 3.79-3.72 (m, 2H), 3.58-3.49 (m, 3H), 3.21 (s, 3H), 3.14 (d, J = 10.3 Hz, 1H) ppm. Mass Spectrum: (ESI) *m/z* 532 $(M+H)^+$.

Example 1450 (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.75 (d, J = 5.8 Hz, 2H), 8.78 (s, 1H), 8.31 (d, J = 8.6 Hz, 1H), 7.68-7.79 (m, 2H), 7.52-7.61 (m, 2H), 7.40 (dd, J = 8.7, 1.9 Hz, 1H), 4.94 (d, J = 16.6 Hz, 1H), 4.59 (d, J = 16.6 Hz, 1H), 4.14 (d, J = 16.4 Hz, 1H), 3.82-3.94 (m, 2H), 3.63-3.68 (m, 1H), 3.43-3.52 (m, 2H), 3.32 (dd, J = 12.6, 3.4 Hz, 1H), 3.14 (s, 3H) ppm. Mass Spectrum: (ESI) *m/z* 516 $(M+H)^+$.

Example 1451 (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.71 (bs, 2H); 8.78 (s, 1H); 8.30 (d, *J* = 8.6 Hz, 1H); 7.73 (bs, 2H); 7.51-7.62 (m, 2H); 7.37-7.44 (m, 2H); 4.94 (d, *J* = 16.5 Hz, 1H); 4.59 (d, *J* = 16.5 Hz, 1H); 4.15 (d, *J* = 16.5 Hz, 1H); 3.90 (d, *J* = 16.5 Hz, 1H); 3.83 (s, 1H); 3.62-3.68 (m, 1H); 3.41-3.52 (m, 2H); 3.32 (AB q, *J* = 12.7, 3.5 Hz, 1H); 3.14 (s, 3H) ppm. Mass Spectrum: (ESI)*m/z* 516 $(M+H)^+$.

Example 1452 (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isopropyl-piperazin-2-one. (RPR 252864A)

For examples where the aryl sulfonamide contains an indole moiety, the compounds were constructed using the above sequence but a Boc-deprotection step was employed at the last step:

A solution of (*R*)-2-[4-(4-amino-quinazolin-7-ylmethyl)-3-isopropyl-5-oxo-piperazine-1-sulfonyl]-6-chloro-indole-1-carboxylic acid tert-butyl ester (102 mg, 0.17 mmol) in CH_2Cl_2 (5 mL) at 0 °C was treated with trifluoroacetic acid 1 mL) and the solution was allowed to warm to ambient temperature and stir for 16 h. The mixture was concentrated to dryness then purified by reverse phase HPLC on a 1" Dynamax, C18 column (5→100% ACN in H_2O/0.1% TFA) to provide 27 mg (25%) of (*R*)-1-(4-amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isopropyl-piperazin-2-one as a white lyophilized solid. ^{1}H NMR (300 MHz, DMSO-d_6) ↗ 12.48 (s, 1H), 9.61 (br s, 2H), 8.74 (s, 1H), 8.26 (d, *J* = 8.5 Hz, 1H), 7.73 (d, *J* = 8.6 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.45-7.52 (m, 2H), 7.12-7.20 (m, 2H), 5.03 (d, *J* = 16.4 Hz, 1H), 4.45 (d, *J* = 16.8 Hz, 1H), 4.00 (d, *J* = 16.3 Hz, 1H), 3.79 (d, *J* = 12.2 Hz, 1H), 3.54 (d, *J* = 16.3 Hz, 1H), 3.30-3.37 (m, 1H), 2.88 (AB quartet, *J* = 12.4, 3.9 Hz, 1H), 2.10-2.18 (m, 1H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H) ppm. Mass Spectrum: (ESI) *m/z* 513 $(M+H)^+$.

The following examples were prepared according to the above procedure:

Example 1453 (*R*)-1-(4-Aminoquinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isopropyl-piperazin-2-one.

^{1}H NMR (300 MHz, DMSO-d_6) ↗ 12.54 (s, 1H), 9.62 (br. s, 2H), 8.74 (s, 1H), 8.26 (d, *J* = 8.6 Hz, 1H), 7.77 (d, *J* = 2.0 Hz, 1H), 7.45-7.61 (m, 3H), 7.34 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.11 (d, *J* =

1.4 Hz, 1H), 5.05 (d, *J* = 16.3 Hz, 1H) 4.45 (d, *J* = 16.3 Hz, 1H), 4.02 (d, *J* = 16.4 Hz, 1H), 3.79 (d, *J* = 16.4 Hz, 1H), 3.55 (d, *J* = 16.4 Hz, 1H), 3.31-3.33 (m, 1H), 2.39 (AB quartet, *J* = 12.5, 3.6 Hz, 1H), 2.08-2.20 (m, 1H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H) ppm. Mass Spectrum: (ESI) *m/z* 513 $(M+H)^+$.

Example 1454 (*S*)-1-(4-Aminoquinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isopropyl-piperazin-2-one.

^{1}H NMR (300 MHz, DMSO-d_6) ↗ 0.95 (dd, *J* = 18.8, 6.8 Hz, 6H), 2.15 (m, 1H), 2.89 (dd, *J* = 12.6, 3.7 Hz, 1H), 3.35 (m, 1H), 3.54 (d, *J* = 16.3 Hz, 1H), 3.80 (d, *J* = 12.3 Hz, 1H), 4.00 (d, *J* = 16.3 Hz, 1H), 4.44 (d, *J* = 16.3 Hz, 1H), 5.03 (d, *J* = 16.3 Hz, 1H), 7.11 (d, *J* = 1.5 Hz, 1H), 7.31 (dd, *J* = 8.9, 2.1 Hz, 1H), 7.51 (m, 2H), 7.57 (d, *J* = 8.6 Hz, 1H), 7.77 (d, *J* = 2.1 Hz, 1H), 8.26 (d, *J* = 8.6 Hz, 1H), 8.73 (s, 1H), 9.59 (br. s, 2H), 12.53 (s, 1H) ppm. Mass Spectrum (ESI)*m/z* 513 $(M+H)^+$.

Example 1455 (*S*)-1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isopropyl-piperazin-2-one.

^{1}H NMR (300 MHz, DMSO-d_6) ↗ 0.95 (dd, *J* = 18.7, 6.8 Hz, 6H), 2.15 (m, 1H), 2.89 (dd, *J* = 12.7, 3.7 Hz, 1H), 3.32 (m, 1H), 3.54 (d, *J* = 16.3 Hz, 1H), 3.83 (d, *J* = 12.3 Hz, 1H), 4.00 (d, *J* = 16.3 Hz, 1H), 4.45 (d, *J* = 16.3 Hz, 1H), 5.04 (d, *J* = 16.3 Hz, 1H), 7.15 (m, 2H), 7.48 (d, *J* = 0.84 Hz, 1H), 7.49 (s, 1H), 7.60 (d, *J* = 7.3 Hz, 1H), 7.72 (d, *J* = 8.6 Hz, 1H), 8.27 (d, *J* = 8.6 Hz, 1H), 8.76 (s, 1H), 9.71 (s, 2H), 12.49 (s, 1H) ppm. Mass Spectrum: (ESI) *m/z* 513 $(M+H)^+$.

Example 1456 (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one.

^{1}H NMR (300 MHz, DMSO-d_6) ↗ 0.79 (dd, *J* = 13.4, 6.4 Hz, 6H), 1.40 (m, 1H), 1.55 (m, 1H), 1.70 (m, 1H), 2.93 (d, *J* = 10.4 Hz, 1H), 3.19 (m, 1H), 3.57 (d, *J* = 16.3 Hz, 1H), 3.69 (d, *J* = 12.4 Hz, 1H), 4.05 (d, *J* = 16.3 Hz, 1H), 5.00 (d, *J* = 16.6 Hz, 1H), 7.13 (d, *J* = 1.4 Hz, 1H), 7.32 (dd, *J* = 8.8, 2.1 Hz, 1H), 7.48 (d, *J* = 4.6 Hz, 1H), 7.50 (s, 1H), 7.57 (d, *J* = 8.6 Hz, 1H), 7.78 (d, *J* = 1.8 Hz, 1H), 8.28 (d, *J* = 8.6 Hz, 1H), 8.74 (s, 1H), 9.63 (s, 2H) ppm. Mass Spectrum (ESI)*m/z* 527 $(M+H)^+$.

Example 1457 (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one.

^{1}H NMR (300 MHz, DMSO-d_6) ↗ 0.79 (dd, *J* = 13.8, 6.4 Hz, 6H), 1.40 (m, 1H), 1.58 (m, 1H), 1.70 (m, 1H), 2.92 (d, *J* = 10.2 Hz, 1H), 3.20 (m, 1H), 3.57 (d, *J* = 16.3 Hz, 1H), 3.69 (d, *J* = 12.2

Hz, 1H), 4.04 (d, *J* = 16.3 Hz, 1H), 4.38 (d, *J* = 16.5 Hz, 1H), 5.01 (d, *J* = 16.5 Hz, 1H), 7.15 (d, *J* = 1.8 Hz, 1H), 7.73 (d, *J* = 8.6 Hz, 1H), 8.27 (d, *J* = 8.6 Hz, 1H), 8.73 (s, 1H), 9.52 (s, 2H) ppm. Mass Spectrum: (ESI) *m/z* 527 $(M+H)^+$.

Example 1458 (*S*)-1-(4-Aminoquinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one.

^{1}H NMR (300 MHz, DMSO-d_6) ↗ 0.79 (dd, *J* = 13.4, 6.4 Hz, 6H), 1.40 (m, 1H), 1.55 (m, 1H), 1.70 (m, 1H), 2.93 (d, *J* = 10.4 Hz, 1H), 3.19 (m, 1H), 3.57 (d, *J* = 16.3 Hz, 1H), 3.69 (d, *J* = 12.4 Hz, 1H), 4.05 (d, *J* = 16.3 Hz, 1H), 4.38 (d, *J* = 16.6 Hz, 1H), 5.00 (d, *J* = 16.6 Hz, 1H), 7.13 (d, *J* = 1.4 Hz, 1H), 7.32 (dd, *J* = 8.8, 2.1 Hz, 1H), 7.48 (d, *J* = 4.6 Hz, 1H), 7.50 (s, 1H), 7.57 (d, 8.6 Hz, 1H), 7.78 (d, *J* = 1.8 Hz, 1H), 8.28 (d, *J* = 8.6 Hz, 1H), 8.74 (s, 1H), 9.63 (s, 2H) ppm. Mass Spectrum: (ESI) *m/z* 527 $(M+H)^+$.

Example 1459 (*S*)-1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one.

^{1}H NMR (300 MHz, DMSO-d_6) ↗ 0.79 (dd, *J* = 13.8, 6.4 Hz, 6H), 1.40 (m, 1H), 1.58 (m, 1H), 1.70 (m, 1H), 2.92 (d, *J* = 10.2 Hz, 1H), 3.20 (m, 1H), 3.57 (d, *J* = 16.3 Hz, 1H), 3.69 (d, *J* = 12.2 Hz, 1H), 4.04 (d, *J* = 16.3 Hz, 1H), 4.38 (d, *J* = 16.5 Hz, 1H), 5.01 (d, *J* = 16.5 Hz, 1H), 7.15 (d, *J* = 1.8 Hz, 1H), 7.18 (d, *J* = 1.8 Hz, 1H), 7.49 (s, 1H), 7.56 (d, *J* = 8.7 Hz, 1H), 7.73 (d, *J* = 8.6 Hz, 1H), 8.27 (d, *J* = 8.6 Hz, 1H), 8.27 (d, *J* = 8.6 Hz, 1H), 8.73 (s, 1H), 9.57 (s, 2H) ppm. Mass Spectrum: (ESI) *m/z* 527 $(M+H)^+$.

Example 1460 (*S*)-1-(4-Aminoquinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-methyl-piperazin-2-one.

^{1}H NMR (300 MHz, DMSO-d_6) ↗ 12.60 (s, 1H), 9.56 (br. s, 2H), 8.75 (s, 1H), 8.28 (d, *J* = 8.6 Hz, 1H), 7.82 (s, 1H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.52 (br. s, 2H), 7.35 (d, *J* = 8.8 Hz, 1H), 7.13 (s, 1H), 4.95 (d, *J* = 16.7 Hz, 1H), 4.53 (d, *J* = 16.7 Hz, 1H), 3.99 (d, *J* = 16.2 Hz, 1H), 3.64 (d, *J* = 16.3 Hz, 2H), 3.16 (d, *J* = 9.5 Hz, 2H), 1.21 (d, *J* = 6.2 Hz, 3H) ppm. Mass Spectrum: (ESI) *m/z* 485 $(M+H)^+$.

Example 1461 (*S*)-1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-methyl-piperazin-2-one.

^{1}H NMR (300 MHz, DMSO-d_6) ↗ 12.5 (s, 1H), 9.54 (br. s, 2H), 8.75 (s, 1H), 8.29 (d, J = 8.5 Hz, 1H), 7.75 (d, J = 8.6 Hz, 1H), 7.58 (d, J = 8.5 Hz, 1H), 7.52 (s, 2H), 7.19 (br. s, 2H), 4.95 (d, J = 16.5 Hz, 1H), 4.52 (d, J = 16.5 Hz, 1H), 4.00 (d, J = 16.4 Hz, 1H), 3.64 (d, J = 16.2 Hz, 2H), 3.14 (d, J = 9.5 Hz, 2H), 1.21 (d, J = 6.1 Hz, 3H) ppm. Mass Spectrum: (ESI) *m/z* 485 $(M+H)^+$.

Example 1462 (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one

Example 1463 (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.55 (s, 1H), 9.67 (bs, 2H), 8.75 (s, 1H), 8.29 (d, J = 8.6 Hz, 1H), 7.77 (d, J = 1.7 Hz, 1H), 7.45-7.59 (m, 3H), 7.31 (dd, J = 8.8, 1.9 Hz, 1H), 7.11 (d, J = 1.4 Hz, 1H), 4.94 (d, J = 16.5 Hz, 1H), 4.56 (d, J = 16.6 Hz, 1H), 4.03 (d, J = 16.3 Hz, 1H), 3.76 (d, J = 12.0 Hz, 1H), 3.42-3.66 (m, 4H), 3.15 (s, 3H), 3.02 (AB q, J = 12.3, 3.1 Hz, 1H) ppm. Mass Spectrum: (ESI) *m/z* 515 $(M+H)^+$.

Example 1464 (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.53 (d, J = 1.7 Hz, 1H), 9.74 (d, J = 14.3 Hz, 2H), 8.73 (s, 1H), 8.30 (d, J = 8.6 Hz, 1H), 7.72 (d, J = 8.6 Hz, 1H), 7.47-7.59 (m, 3H), 7.11-7.18 (m, 2H), 4.94 (d, J = 16.7 Hz, 1H), 4.55 (d, J = 16.4 Hz, 1H), 3.76 (d, J = 12.0 Hz, 1H), 3.43-3.64 (m, 4H), 3.14 (s, 3H), 3.02 (AB q, J = 12.3, 3.29 Hz, 1H) ppm Mass Spectrum: (ESI) *m/z* 515 $(M+H)^+$.

Example 1465 (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one

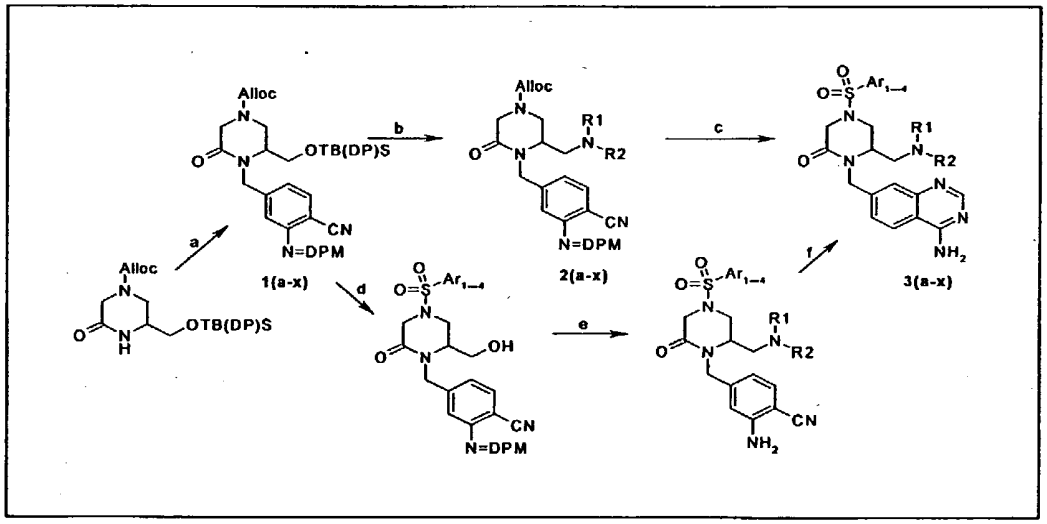
^{1}H NMR (300 MHz, DMSO-d_6) δ 12.48 (s, 1H); 9.63 (bs, 2H); 8.75 (s, 1H); 8.27 (d, J = 8.5 Hz, 1H); 7.73 (d, J = 8.6 Hz, 1H); 7.56 (d, J = 8.8 Hz, 1H); 7.48 (s, 2H); 7.13-7.20 (m, 2H); 4.95 (d, J = 16.5 Hz, 1H); 4.56 (d, J = 16.7 Hz, 1H); 4.03 (d, J = 15.9 Hz, 1H); 3.76 (d, J = 12.7 Hz, 1H); 3.44-3.65 (m, 4H); 3.16 (s, 3H); 3.00 (AB q, J = 11.7, 2.6 Hz, 1H) ppm. Mass Spectrum: (ESI) *m/z* 515 $(M+H)^+$.

Example 1466 (*S*)-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-yl]-acetic acid

A: (*S*)-[2-(4-Amino-quinazolin-7-ylmethyl)-5-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-yl]-acetic acid. To a solution of (*S*)-[2-(4-amino-quinazolin-7-ylmethyl)-5-(6-chloro-

benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-yl]-acetic acid tert-butyl ester (58 mg, 0.096 mmol) in CH_2Cl_2 cooled to 0°C was added TFA (1 mL). After stirring for 30 min. at 0°C the reaction was allowed to warm to room temperature. After stirring for 2 h the solvent was concentrated and the residue dissolved in water. Lyophilization afforded 53 mg (82%) of (*S*)-[2-(4-amino-quinazolin-7-ylmethyl)-5-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-yl]-acetic acid as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.52 (bs, 2H), 8.74 (s, 1H), 8.34 (d, *J* = 1.8 Hz, 1H), 8.27 (d, *J* = 8.5 Hz, 1H), 8.21 (s, 1H), 8.07 (d, *J* = 8.7 Hz, 1H), 7.50-7.60 (m, 3H), 5.02 (d, *J* = 16.4 Hz, 1H), 4.50 (d, *J* = 16.4 Hz, 1H), 3.72-3.81 (m, 2H), 3.63 (d, *J* = 16.2 Hz, 1H), 3.14-3.21 (m, 1H), 2.70-2.80 (m, 2H) ppm. Mass Spectrum: (ESI)*m/z* 546 $(M+H)^+$.

Scheme 5 A synthetic scheme of the C(6)-alkylaminomethyl substituted sulfonamide inhibitors.



Reagents: (a). NaH, 4-Bromomethyl-2-diphenylmethyleneaminobenzonitrile, THF. (b). 1. TBAF, THF. 2. SO3-Py, DMSO. 3. amines, $NaB(OAc)_3H$, 4A MS. (c). 1. $Pd(PPh_3)_4$, morpholine, CH_2Cl_2. 2. "Sulfonyl chloride", Et_3N, CH_2Cl_2. 3. c-HCl, MeOH. 4. 1,3,5-Triazine, AcOH, EtOH, reflux. (d). 1. see (c.1-2, b.1) (e). 1. Dess-Martin. 2. see (b3, c.3) (f) see (c.4).

Example 1467 (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-(4-methyl-piperazin-1-ylmethyl)-piperazin-2-one (RPR257023A)

A: (*R*)-4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-(tert-butyl-diphenyl-silanyloxy methyl)-5-oxo-piperazine-1-carboxylic acid allyl ester. To a solution of (*R*)-3-(tert-butyl-diphenyl-silanyloxymethyl)-5-oxo-piperazine-1-carboxylic acid allyl ester (5.2 g, 11.5 mmol) in a mixture of 5:1 THF:DMF (120 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 0.6 g, 15 mmol) followed after 15 min by 2-(benzhydrylidene-amino)-4-bromomethyl-benzonitrile (4.7

g, 12.7 mmol). After 2 h at ambient temperature the reaction mixture was diluted with saturated NH_4Cl, and extracted with EtOAc. The extracts were washed with water (twice), dried ($MgSO_4$), filtered and concentrated. The crude residue was used in the next reaction without further purification. Mass Spectrum: (ESI) *m/z* 747 $(M+H)^+$.

B: (*S*)-4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-(4-methyl-piperazin-1-ylmethyl)-5-oxo-piperazine-1-carboxylic acid allyl ester. A solution of (*R*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-(tert-butyl-diphenyl-silanyloxy methyl)-5-oxo-piperazine-1-carboxylic acid allyl ester in THF (100 mL) was treated with a 1.0 M solution of TBAF in THF (17 mL, 17 mmol). After 0.5 h at ambient temperature, the reaction mixture was diluted with saturated NH_4Cl and extracted with EtOAc. The extracts were dried ($MgSO_4$), filtered and concentrated. The crude residue was chromatographed on SiO_2 (hexanes / EtOAc, 1:1 to 1:5) to yield 4.3 g (50%) of (*R*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-hydroxymethyl-5-oxo-piperazine-1-carboxylic acid allyl ester. Mass Spectrum: (ESI) *m/z* 509 $(M+H)^+$.

A solution of (*R*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-hydroxymethyl-5-oxo-piperazine-1-carboxylic acid allyl ester (2.4 g, 4.7 mmol) in DMSO (8 mL) and Et_3N (4 mL) at 0 °C was treated with SO_3.Py (3.76 g, 24 mmol). After 20 h at ambient temperature, the mixture was diluted with water, and extracted with EtOAc. The extracts were washed with saturated NH_4Cl solution and water, dried ($MgSO_4$) and concentrated. The crude (*R*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-formyl-5-oxo-piperazine-1-carboxylic acid allyl ester (~2.3 g) was used in the next reaction without further purification. Mass Spectrum: (ESI) *m/z* 507 $(M+H)^+$.

To a mixture of (*R*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-formyl-5-oxo-piperazine-1-carboxylic acid allyl ester (100 mg, 0.2 mmol), N-methylpiperazine (0.066 mL, 0.59 mmol) and powdered 4Å MS (0.1 g) in 1,2-dichloroethane (2 mL) at 0 °C was added sodium triacetoxy-borohydride (0.13 g, 0.6 mmol). After 20 h at ambient temperature, the reaction mixture was quenched with saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2. The extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated. Chromatography on SiO_2 (2% to 10% MeOH in CH_2Cl_2) provided 50 mg (43%) of (*S*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-(4-methyl-piperazin-1-ylmethyl)-5-oxo-piperazine-1-carboxylic acid allyl ester. ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.1 Hz, 2H), 7.5-7.1 (m, 9H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.59 (s, 1H), 6.0-5.85 (m, 1H), 5.35-5.23 (m, 3H), 4.7-4.55 (m, 2H), 4.5-4.5 (m, 1H), 4.23 (d, *J* = 15 Hz, 1H), 4.0-3.8 (m, 2H), 3.0-2.8 (m, 2H), 2.5-2.3 (m, 10H), 2.28 (s, 3H) ppm. Mass Spectrum: (ESI) *m/z* 591 $(M+H)^+$.

C: (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-(4-methyl-piperazin-1-ylmethyl)-piperazin-2-one. Tetrakis(triphenylphosphine)palladium(0) (21 mg, 0.02 mmol) was added to a solution of (*S*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-(4-methyl-piperazin-1-ylmethyl)-5-oxo-piperazine-1-carboxylic acid allyl ester (50 mg, 0.085 mmol) and morpholine (0.074 mL, 0.85 mmol) in CH_2Cl_2 (5 mL). After 1 h at ambient temperature, the reaction mixture was concentrated and chromatographed on SiO_2 (5% to 15% MeOH inCH_2Cl_2) to provide 40 mg (93%) of (*S*)-2-(benzhydrylidene-amino)-4-[2-(4-methyl-piperazin-1-ylmethyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile: Mass Spectrum: (ESI) *m/z* 507 $(M+H)^+$.

To a solution of (*S*)-2-(benzhydrylidene-amino)-4-[2-(4-methyl-piperazin-1-ylmethyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile (40 mg, 0.08 mmol) in CH_2Cl_2 (3 mL) at 0 °C was added Et_3N (0.055 mL, 0.4 mmol), followed by 6-chloro-benzo[b]thiophene-2-sulfonyl chloride (30 mg, 0.12 mmol). After 1 h at ambient temperature, the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The extracts were washed with saturated NH_4Cl solution and brine, dried ($MgSO_4$), filtered, and concentrated. The crude residue was used in the next reaction without further purification. Mass Spectrum: (ESI)*m/z* 737 $(M+H)^+$.

Concentrated HCl (12M, 5 drops) was added to a solution of (*S*)-2-(benzhydrylidene-amino)-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-(4-methyl-piperazin-1-ylmethyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile in MeOH (5 mL) at 0 °C. After 1 h at ambient temperature, the reaction mixture was concentrated and partitioned between EtOAc and saturated $NaHCO_3$ solution. The separated organic phase was washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude residue was chromatographed on SiO_2 (10% to 20% MeOH in CH_2Cl_2) to provide 20 mg (44%) of (*S*)-2-amino-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-(4-methyl-piperazin-1-ylmethyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile. Mass Spectrum: (ESI) *m/z* 573 $(M+H)^+$.

To a solution of (*S*)-2-amino-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-(4-methyl-piperazin-1-ylmethyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile (20 mg, 0.035 mmol) in absolute ethanol (3 mL) was added 1,3,5-triazine (28 mg, 0.35 mmol) and acetic acid (0.02 mL, 0.35 mmol). The solution was heated to a reflux. After 48 h, the solution was concentrated and the resulting crude product was chromatographed on SiO_2 (10% to 30% MeOH in CH_2Cl_2) to provide 15 mg (71%) of (*S*)-1-(4-amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-(4-methyl-piperazin-1-ylmethyl)-piperazin-2-one. Mass Spectrum: (ESI) *m/z* 600 $(M+H)^+$.

The following compounds were prepared according to the above procedures using the appropriate amines and sulfonyl chlorides.

Example	Compound Name	*m/z* (M+H)
1468	(*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzo imidazole-2-sulfonyl)-6-pyrrolidin-1-ylmethyl-piperazin-2-one	555
1469	(*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b] thiophene-2-sulfonyl)-6-pyrrolidin-1-ylmethyl-piperazin-2-one	
1470	(6S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b] thiophene-2-sulfonyl)-6-{[(2-dimethylamino-ethyl)-methyl-amino]-methyl}-piperazin-2-one	602

Example 1471 (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-(4-pyrrolidin-1-yl-piperidin-1-ylmethyl)-piperazin-2-one (RPR257982A).

A: (*R*)-4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-(tert-butyl-dimethyl-silanyloxymethyl)-5-oxo-piperazine-1-carboxylic acid allyl ester. To a solution of (R)-3-(tert-butyl-dimethyl-silanyloxymethyl)-5-oxo-piperazine-1-carboxylic acid allyl ester (2.5 g, 7.62 mmol) in a mixture of THF (40 mL) and DMF (2 mL) at 0°C was added NaH 60% dispersion in mineral oil (400 mg, 9.91 mmol). After stirring for 10 min 2-(benzhydrylidene-amino)-4-bromomethyl-benzonitrile (2.81 g, 7.62 mmol) was added in one portion. More NaH (63 mg, 1.5 mmol) was added after 1 h. After stirring for an additional 1 h the reaction was quenched with aq. NH_4Cl and extracted with ether. The ether was washed with brine, dried over Na_2SO_4, filtered and concentrated. Chromatography on SiO_2 (CH_2Cl_2 to 1% MeOH / CH_2Cl_2) afforded 3.90 g (82%) of (*R*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-(tert-butyl-dimethyl-silanyloxymethyl)-5-oxo-piperazine-1-carboxylic acid allyl ester as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.3 Hz, 2H), 7.38-7.50 (m, 4H), 7.25-7.28 (m, 3H), 7.17 (br s, 2H), 6.86 (dd, *J* = 8.0, 0.9 Hz, 1H), 6.59 (s, 1H), 5.84-5.98 (m, 1H), 5.20-5.35 (m, 3H), 4.60 (s, 2H), 4.27-4.39 (m, 1H), 4.13 (d, *J* = 13.4 Hz, 1H), 3.90 (d, *J* = 15.2 Hz, 2H), 3.54 (br s, 2H), 3.00-3.05 (m, 1H), 2.84-2.95 (m, 1H), 0.87 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H) ppm. Mass Spectrum: (ESI) *m/z* 623 $(M+H)^+$.

B: (*R*)-2-(Benzhydrylidene-amino)-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-hydroxymethyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile. To a solution of (*R*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-(tert-butyl-dimethyl-silanyloxymethyl)-5-oxo-piperazine -1-carboxylic acid allyl ester (3.90 g, 6.27 mmol) and morpholine (2.75 mL, 31 mmol) in CH_2Cl_2 (60 mL) was added $(PPh_3)_4Pd$ (728 mg, 0.630 mmol). After stirring for 20 min the

reaction was chromatographed on SiO_2 (CH_2Cl_2 to 2% MeOH / CH_2Cl_2) to give 3.0 g (89%) of (*R*)-2-(benzhydrylidene-amino)-4-[2-(tert-butyl-dimethyl-silanyloxymethyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile as a yellow oil. Mass Spectrum: (ESI) *m/z* 539 $(M+H)^+$.

To a solution of (*R*)-2-(benzhydrylidene-amino)-4-[2-(tert-butyl-dimethyl-silanyloxymethyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile (3.0 g, 5.57 mmol) and DIPEA (1.3 mL, 7.24 mmol) in CH_2Cl_2 at 0 °C was added 6-chloro-benzo[b]thiophene-2-sulfonyl chloride (1.50 g, 5.57 mmol). The reaction was allowed to warm to ambient temperature for 16 h and was concentrated. Chromatography on SiO_2 (Hexanes to 2:1 Hexanes / EtOAc) afforded 3.29 g (76%) of (*R*)-2-(benzhydrylidene-amino)-4-[2-(tert-butyl-dimethyl-silanyloxymethyl)-4-(6-chloro-benzo[b] thiophene-2-sulfonyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile as a yellow solid. Mass Spectrum: (ESI) *m/z* 769 $(M+H)^+$.

To a solution of (*R*)-2-(benzhydrylidene-amino)-4-[2-(tert-butyl-dimethyl-silanyloxymethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile (3.16 g, 4.11 mmol) in THF (20 mL) at 0 °C was added TBAF (5.4 mL of a 1 M solution in THF, 5.4 mmol). After 15 min. the reaction was complete and chromatography on SiO_2 (CH_2Cl_2 to 2% MeOH / CH_2Cl_2) afforded 2.42 g (90%) of (*R*)-2-(benzhydrylidene-amino)-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-hydroxymethyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile as a yellow foam. ^1H NMR (300 MHz, $CDCl_3$) δ 7.85-7.87 (m, 1H), 7.82 (d, *J* = 2.9 Hz, 1H), 7.72 (d, *J* = 7.3 Hz, 2H), 7.37-7.51 (m, 6H), 7.09-7.23 (m, 5H), 6.81 (dd, *J* = 7.9, 1.5 Hz, 1H), 6.55 (d, *J* = 1.3 Hz, 1H), 4.98 (d, *J* = 15.1 Hz, 1H), 4.20 (d, *J* = 16.6 Hz, 1H), 4.03 (d, *J* = 15.1 Hz, 1H), 3.94 (d, *J* = 12.3 Hz, 1H), 3.59-3.72 (m, 2H), 3.51 (d, *J* = 16.7 Hz, 1H), 3.12-3.19 (m, 1H), 2.65 (dd, *J* = 12.4, 3.17 Hz, 1H), 2.23 (t, *J* = 5.4 Hz, 1H) ppm. Mass Spectrum: (ESI) *m/z* 655 $(M+H)^+$.

C: (*S*)-2-Amino-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-6-(4-pyrrolidin-1-yl-piperidin-1-ylmethyl)-piperazin-1-ylmethyl]-benzonitrile. To a solution of (*R*)-2-(benzhydrylidene-amino)-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-hydroxymethyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile (1.3 g, 2.0 mmol) in CH_2Cl_2 (20 mL) was added Dess-Martin Periodinane (1.77 g, 4.1 mmol). After stirring for 30 min the reaction was chromatographed on SiO_2 (CH_2Cl_2 to 1% MeOH / CH_2Cl_2) to afford 975 mg (75%) of (*R*)-2-(benzhydrylidene-amino)-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-formyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile as a yellow solid. ^1H NMR (300 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.25 (dd, *J* = 7.6, 1.5 Hz, 2H), 7.66-8.01 (m, 8H), 7.11-7.48 (m, 5H), 6.76 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.51 (d, *J* = 1.2 Hz, 1H), 5.20 (d, *J* = 15.1 Hz, 1H), 4.17-4.28 (m, 2H), 3.84 (d, *J* = 15.1 Hz, 1H), 3.40-3.52 (m, 2H), 2.82 (dd, *J* = 12.8, 4.0 Hz, 1H) ppm.

To a solution of (*R*)-2-(benzhydrylidene-amino)-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-formyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile (440 mg, 0.674 mmol), 4-(1-pyrrolidinyl)-piperidine (422 mg, 2.73 mmol), and 4Å molecular sieves (725 mg) in 1,2-dichloroethane (10 mL) was added $NaBH(OAc)_3$ (432 mg, 2.04mmol). After stirring for 16 h the molecular sieves were filtered off and washed with CH_2Cl_2. The filtrate was then washed with aq. NH_4Cl, followed by brine, dried over Na_2SO_4, filtered, and concentrated to give 289 mg (54%) of (*S*)-2-(benzhydrylidene-amino)-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-6-(4-pyrrolidin-1-yl-piperidin-1-ylmethyl)-piperazin-1-ylmethyl]-benzonitrile as a yellow solid. Mass Spectrum: (ESI) m/z 791 $(M+H)^+$.

To a solution of (*S*)-2-(benzhydrylidene-amino)-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-6-(4-pyrrolidin-1-yl-piperidin-1-ylmethyl)-piperazin-1-ylmethyl]-benzonitrile (289 mg, 0.365 mmol) in a mixture of MeOH (4 mL) and THF (2 mL) at 0°C was added conc. HCl (3 drops). After stirring for 20 min, $NaHCO_3$ was added and the reaction was concentrated to dryness. The residue was chromatographed on SiO_2 (CH_2Cl_2 to 5% MeOH / CH_2Cl_2) to afford 96 mg (42%) of (*S*)-2-amino-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-6-(4-pyrrolidin-1-yl-piperidin-1-ylmethyl)-piperazin-1-ylmethyl]-benzonitrile as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.79-7.87 (m, 3H), 7.43 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 6.66 (s, 1H), 6.33-6.40 (m, 1H), 5.14 (d, *J* = 15.1 Hz, 1H), 4.24 (d, *J* = 16.1 Hz, 1H), 3.94-4.09 (m, 2H, 3.73 (br s, 1H), 3.54-3.69 (m, 2H), 3.48 (d, *J* = 16.6 Hz, 1H), 3.30-3.38 (m, 2H), 2.72-3.06 (m, 5H), 2.64-2.70 (m, 1H), 2.19-2.32 (m, 2H), 1.97-2.15 (m, 8H) ppm. Mass Spectrum: (ESI) *m/z* 627 $(M+H)^+$.

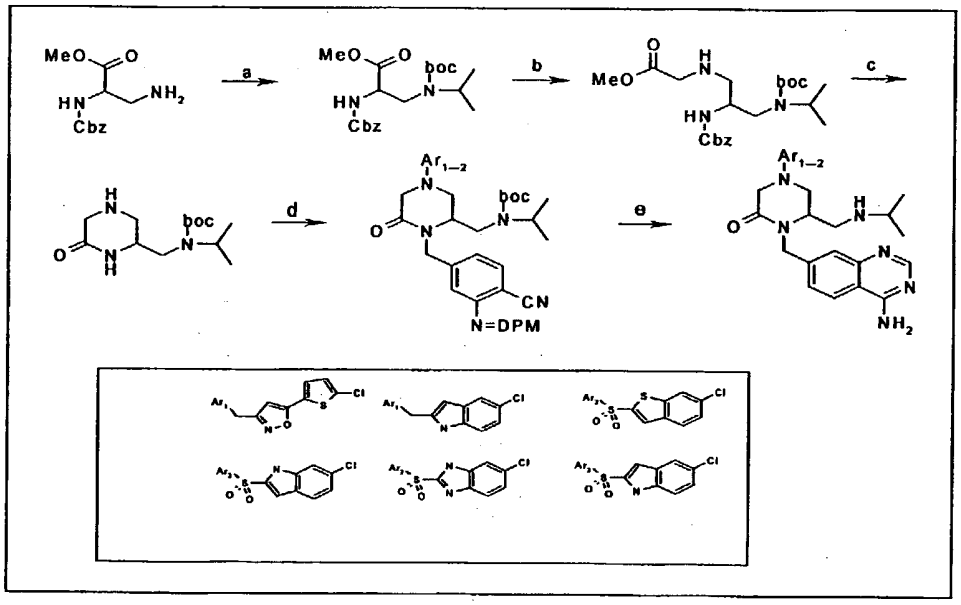
D: (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-(4-pyrrolidin-1-yl-piperidin-1-ylmethyl)-piperazin-2-one. A mixture of (*S*)-2-amino-4-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-6-(4-pyrrolidin-1-yl-piperidin-1-ylmethyl)-piperazin-1-ylmethyl]-benzonitrile (96 mg, 0.153 mmol), HOAc (88 μL, 1.53 mmol), and 1,3,5-triazine (143 mg, 1.76 mmol) in absolute EtOH (6 mL) was refluxed overnight. The crude material was purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 80% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions were combined and lyophilized to give 106 mg (90%) of the TFA salt of (*S*)-1-(4-amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-(4-pyrrolidin-1-yl-piperidin-1-ylmethyl)-piperazin-2-one as a white solid. ^1H NMR (300 MHz, CD_3OD) δ 8.61 (s, 1H), 8.24 (d, *J* = 8.6 Hz, 1H), 8.09 (d, *J* = 1.9 Hz, 1H), 7.97-8.05 (m, 2H), 7.62 (dd, 8.6, 1.4 Hz, 1H), 7.49-7.57 (m, 2H), 5.14 (d, *J* = 16.5 Hz, 1H), 4.60 (d, *J* = 16.4 Hz, 1H), 4.17-4.32 (m, 2H), 3.70-3.76 (m, 1H), 3.57-3.67 (m, 3H), 3.09-

3.18 (m, 5H), 2.94-3.05 (m, 2H), 2.75-2.79 (m, 1H), 2.33-2.48 (m, 2H) ppm. Mass Spectrum: (ESI) *m/z* 654 $(M+H)^+$.

The following compounds were prepared according to the above procedures using the appropriate amines and 6-chloro-benzo[b]thiophene-2-sulfonyl chloride.

Example	Compound Name	*m/z* (M+H)
1472	(*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b] thiophene-2-sulfonyl)-6-[([1,3]dioxolan-2-ylmethyl-methyl-amino)-methyl]-piperazin-2-one	617
1473	(*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b] thiophene-2-sulfonyl)-6-(4-pyrrolidin-1-yl-piperidin-1-ylmethyl)-piperazin-2-one	654
1474	(*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b] thiophene-2-sulfonyl)-6-[(2-isopropoxy-ethylamino)-methyl]-piperazin-2-one	603
1475	(*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b] thiophene-2-sulfonyl)-6-[(cyclopentyl-methyl-amino)-methyl]-piperazin-2-one	599

Scheme 6 A synthetic scheme of the C(6)-isopropyl substituted inhibitors.



Reagents: (a) 1. Acetone, $NaBH_3CN$, MeOH; 2. Boc_2O, DMAP, THF; (b) 1. "$CaBH_4$", EtOH; 2. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C; 3. Gly-OMe.HCl, $NaBH_3CN$, MeOH; (c) H_2, MeOH, 10% Pd / C; (d) 1. Alloc-Cl, Et_3N, CH_2Cl_2; 2. NaH, 2-(benzyhydrylidene-amino)-4-bromomethyl-

benzonitrile, THF; 3. $Pd(PPh_3)_4$, Morpholine, CH_2Cl_2; 4. Sulfonyl chloride / Aryl bromide, Et_3N, CH_2Cl_2; (e) 1. Conc. HCl, MeOH; 2. 1,3,5-Triazine, AcOH, EtOH, Reflux.

Example 1476. (*S*)-1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isopropylaminomethyl)piperazin-2-one

A: (*S*)-3-Amino-2-benzyloxycarbonylamino-propionic acid methyl ester hydrochloride. Thionyl chloride (4.48 mL, 61.34 mmol) was added cautiously to anhydrous methanol (50 mL) at 0 °C. After 5 min, 3-amino-2-benzyloxycarbonylamino-propionic acid (14.6 g, 61.34 mmol) was added. The heterogeneous mixture was allowed to warm to ambient temperature (became homogeneous) then warmed to reflux for 2.5 h. The cooled mixture was concentrated and dried *in vacuo* to afford 16 g (90%) of (*S*)-3-amino-2-benzyloxycarbonylamino-propionic acid methyl ester hydrochloride as a white solid which was used without purification. ^{1}H NMR (300 MHz, DMSO-d_6) ↗ 3.08 (m, 1H), 3.20 (m, 1H), 3.65 (s, 3H) 4.42 (m, 1H), 5.05 (s, 2H), 7.3 (br. s, 5H), 7.89 (d, *J* = 8.3 Hz, 1H), 8.20 (br. s, 2H) ppm. Mass Spectrum: (ESI) *m/z* 253 $(M+H)^+$.

B: (*S*)-2-Benzyloxycarbonylamino-3-isopropylamino-propionic acid methyl ester. To a solution of (*S*)-3-amino-2-benzyloxycarbonylamino-propionic acid methyl ester hydrochloride (5 g, 17.33 mmol) in anhydrous MeOH (50 mL) at 0 °C was added acetone (1.15 mL, 15.6 mmol) followed by sodium cyanoborohydride (26 mL, 1.0 M / THF, 26 mmol). The mixture was stirred at ambient temperature for 4 h then acetone (0.5 mL, 13 mmol) was added and the mixture was left to stir for a further 16 h. The mixture was concentrated to dryness then partitioned between aqueous $NaHCO_3$ (200 mL) and EtOAc (200 mL). The aqueous layer was extracted with EtOAc (2 x 100 mL) and the combined organic phases were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated to afford a grey oil.

The crude product was purified by flash silica gel chromatography (CH_2Cl_2→1% MeOH / CH_2Cl_2) to afford 2.96 g (58%) of (*S*)-2-benzyloxycarbonylamino-3-isopropylamino-propionic acid methyl ester as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) ↗ 0.99 (d, *J* = 6.3 Hz, 6H), 1.15 (m, 1H), 2.75 (m, 1H), 2.91 (dd, *J* = 12.5, 4.5 Hz, 1H), 3.03 (dd, *J* = 12.5, 4.5 Hz, 1H), 3.70 (s, 3H), 4.40 (m, 1H), 5.10 (s, 2H), 5.70 (m, 1H), 7.30 (br. s, 5H) ppm. Mass Spectrum: (ESI) m/z 294 $(M+H)^+$.

C: (*S*)-2-Benzyloxycarbonylamino-3-(tert-butoxycarbonyl-isopropyl-amino)-propionic acid methyl ester. To a solution of (*S*)-2-benzyloxycarbonylamino-3-isopropylamino-propionic acid methyl ester (2.96 g, 10.07 mmol) in anhydrous THF (50 mL) at 0 °C was added DMAP (100

mg) followed by Boc-anhydride (2.42 g, 11.07 mmol). The solution was allowed to stir at ambient temperature for 16 h then was concentrated to dryness. The crude product was purified by flash silica gel chromatography (CH_2Cl_2→1% MeOH / CH_2Cl_2→2%→5%) to afford 5.0 g (65%) of (*S*)-2-benzyloxycarbonylamino-3-(tert-butoxycarbonyl-isopropyl-amino)-propionic acid methyl ester as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) ↗ 1.16 (d,*J* = 3.8 Hz, 6H) 1.45 (s, 9H), 3.40 (m, 2H), 3.70 (s, 3H), 4.00 (m, 1H), 4.40 (br. s, 1H), 5.50 (s, 2H), 6.10 (br. s, 1H), 7.30 (br. s, 5H) ppm. Mass Spectrum: (ESI) *m/z* 394 M^+.

D: (*S*)-[2-(tert-Butoxycarbonyl-isopropyl-amino)-1-hydroxymethyl-ethyl]-carbamic acid benzyl ester. To a stirring suspension of freshly ground sodium borohydride (1.92 g, 50.76 mmol) in abs. EtOH (100 mL) at -40 °C was added calcium chloride (2.82 g, 25.38 mmol). The heterogeneous mixture was stirred at -20 °C for 45 min then a solution of (*S*)-2-benzyloxycarbonylamino-3-(tert-butoxycarbonyl-isopropyl-amino)-propionic acid methyl ester (5.0 g, 12.69 mmol) in abs. EtOH (50 mL) was added via pipette. The mixture was stirred at -20 °C for 1 h then was quenched with water (200 mL) and acidified cautiously to ~pH 3 with 2N HCl. The mixture was then extracted with CH_2Cl_2 (3 x 200 mL) and the combined organic phases were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated to afford a colourless oil.

The crude product was purified by flash silica gel chromatography (CH_2Cl_2→1% MeOH / CH_2Cl_2→2%→5%) to afford 4.14 g (95%) of (*S*)-[2-(tert-butoxycarbonyl-isopropyl-amino)-1-hydroxymethyl-ethyl]-carbamic acid benzyl ester as a colourless oil. ^{1}H NMR (300 MHz, CDCl3) ↗ 1.19 (dd, *J* = 18.7, 6.7 Hz, 6H), 1.45 (s, 9H), 3.10 (m, 1H), 3.50 (m, 2H), 3.61 (m, 2H), 4.00 (m, 1H), 4.20 (m, 1H), 5.10 (s, 2H), 5.50 (m, 1H), 7.30 (br. s, 5H) ppm. Mass Spectrum: (ESI) *m/z* 366 M^+.

E: (*S*)-[2-Benzyloxycarbonylamino-3-(tert-butoxycarbonyl-isopropyl-amino)-propylamino]-acetic acid methyl ester. To a solution of oxalyl chloride (1.18 mL, 13.57 mmol) in anhydrous CH_2Cl_2 (40 mL) at -78 ° C was added DMSO (1.93 mL, 27.14 mmol) dropwise. The solution was stirred at -78 °C for 10 min then a solution of (*S*)-[2-(tert-butoxycarbonyl-isopropyl-amino)-1-hydroxymethyl-ethyl]-carbamic acid benzyl ester (4.14 g, 11.31 mmol) in anhydrous CH_2Cl_2 (80 mL) was added via pipette. The reaction was stirred at -78 °C for 1 h then triethylamine (7.88 mL, 56.55 mmol) was added and the reaction stirred at 0 °C for 10 min. The mixture was partitioned between $NaHSO_4$ (200 mL) and CH_2Cl_2 (200 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic phases were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated to afford (*S*)-[2-(tert-butoxycarbonyl-

isopropyl-amino)-1-formyl-ethyl]-carbamic acid benzyl ester as a yellow oil which was used immediately without purification.

To a solution of (*S*)-[2-(tert-butoxycarbonyl-isopropyl-amino)-1-formyl-ethyl]-carbamic acid benzyl ester (11.31 mmol) in anhydrous MeOH (80 mL) at 0 °C was added glycine methyl ester hydrochloride (5.68 g, 45.24 mmol). The solution was stirred at 0 °C for 10 min then sodium cyanoborohydride (16.97 mL, 1.0 M / THF, 16.97 mmol) was added and the heterogeneous mixture was warmed to ambient temperature and stirred for 16 h. The mixture was concentrated to dryness and partitioned between aqueous $NaHCO_3$ (100 mL) and EtOAc (100 mL). The aqueous layer was extracted with EtOAc (3 x 100 mL) and the combined organic phases were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated to afford 4.75 g (96%) of *(S)*-[2-benzyloxycarbonylamino-3-(tert-butoxycarbonyl-isopropyl-amino)-propyl amino]-acetic acid methyl ester as a colourless oil which was used in the next step without purification. Mass Spectrum (ESI) *m/z* 438 $(M+H)^+$.

F: (*S*)-Isopropyl-(6-oxo-piperazin-2-ylmethyl)-carbamic acid tert-butyl ester. A solution of *(S)*-[2-benzyloxycarbonylamino-3-(tert-butoxycarbonyl-isopropyl-amino)-propyl amino]-acetic acid methyl ester (2.58 g, 5.9 mmol) in MeOH (150 mL) was placed in a large Parr bottle and treated with 10% palladium on carbon (300 mg) under N_2 atmosphere. The mixture was hydrogenated at 40 psi for 5 h then filtered through celite. The filtrate was concentrated to afford 1.60 g (100%) of (*S*)-isopropyl-(6-oxo-piperazin-2-ylmethyl)-carbamic acid tert-butyl ester as a grey oil which was used without further purification. Mass Spectrum (ESI) *m/z* 272 $(M+H)^+$.

G: (*S*)-3-[(tert-Butoxycarbonyl-isopropyl-amino)-methyl]-5-oxo-piperazine-1-carboxylic acid allyl ester. To a solution of (*S*)-isopropyl-(6-oxo-piperazin-2-ylmethyl)-carbamic acid tert-butyl ester (1.6 g, 5.9 mmol) in anhydrous CH_2Cl_2 (100 mL) at 0 °C was added triethylamine (1.23 mL, 8.85 mmol) followed by allyl chloroformate (0.75 mL, 7.08 mmol). The solution was stirred at ambient temperature for 16 h then partitioned between $NaHCO_3$ (100 mL) and CH_2Cl_2 (100 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL) and the combined organic phases were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash silica gel chromatography and dried in vacuo to afford 1.51 g (72%) of (*S*)-3-[(tert-butoxycarbonyl-isopropyl-amino)-methyl]-5-oxo-piperazine-1-carboxylic acid allyl ester as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$) ↗ 1.12 (dd, *J* = 6.8, 3.7 Hz, 6H), 1.45 (s, 9H), 3.10 (m, 1H), 3.20 (m, 2H), 3.70 (m, 2H), 3.85 (m, 2H), 4.11 (ABq,*J* = 47.2, 18.2 Hz, 2H), 4.62 (d, *J* = 5.6 Hz, 2H), 5.30 (m, 2H), 5.90 (m, 1H) ppm. Mass Spectrum: (ESI)*m/z* 356 $(M+H)^+$.

H: (*S*)-4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-[(tert-butoxycarbonyl-isopropyl-amino)-methyl]-5-oxo-piperazine-1-carboxylic acid allyl ester. To a solution of (*S*)-3-[(tert-butoxycarbonyl-isopropyl-amino)-methyl]-5-oxo-piperazine-1-carboxylic acid allyl ester (1.51 g, 4.25 mmol) in a mixture of anhydrous THF (100 mL) and anhydrous DMF (10 mL) at 0 °C was added sodium hydride (0.2 g, 60% dispersion / oil, 5.1 mmol). The mixture was stirred at 0 °C for 30 min until gas evolution ceased, then 2-(benzyhydrylidene-amino)-4-bromomethyl-benzonitrile (1.75 g, 4.68 mmol) was added. The brown mixture was stirred at 0-10 °C for 3 h then partitioned between saturated aqueous NH_4Cl (200 mL) and EtOAc (200 mL). The aqueous layer was extracted with EtOAc (2 x 100 mL) and the combined organic phases were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated to afford a brown oil. The crude product was purified by flash silica gel chromatography to afford 2.76 g (100%) of (*S*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-[(tert-butoxycarbonyl-isopropyl-amino)-methyl]-5-oxo-piperazine-1-carboxylic acid allyl ester as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$) ↗ 1.15 (m, 6H), 1.45 (s, 9H), 2.65 (m, 1H), 3.00 (m, 1H), 3.35 (m, 2H), 3.50 (m, 1H), 3.90 (m, 9H), 4.32 (d, *J* = 18.5 Hz, 1H), 4.63 (d, *J* = 5.5 Hz, 2H), 5.30 (m, 2H), 5.95 (m, 1H), 6.80 (br. s, 1H), 7.0 (br. s, 1H), 7.20 (br. s, 5H), 7.40 (br. s, 5H), 7.80 (m, 1H) ppm. Mass Spectrum: (ESI) *m/z* 650 $(M+H)^+$.

I: (*S*)-{1-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-6-oxo-piperazin-2-ylmethyl}-isopropyl-carbamic acid tert-butyl ester. To a solution of (*S*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-[(tert-butoxycarbonyl-isopropyl-amino)-methyl]-5-oxo-piperazine-1-carboxylic acid allyl ester (2.76 g, 4.28 mmol) in anhydrous CH_2Cl_2 (250 mL) was added morpholine (1.87 mL, 21.4 mmol) followed by *tetrakis* (triphenylphosphine) palladium (495 mg, 0.43 mmol). The yellow solution was stirred at ambient temperature for 1 h then concentrated on to silica gel and flash column chromatographed (CH_2Cl_2→1% MeOH / CH_2Cl_2→2%→3%→5%) to afford 1.9 g (79%) of (*S*)-{1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-6-oxo-piperazin-2-ylmethyl}-isopropyl-carbamic acid tert-butyl ester as a yellow foam. ^1H NMR (300 MHz, $CDCl_3$) ↗ 1.08 (t, *J* = 6.8 Hz, 6H), 1.45 (s, 9H), 2.42 (m, 1H), 2.69 (m, 1H), 2.90 (m, 2H), 3.18 (m, 1H), 3.57 (d, *J* = 9.7 Hz, 2H), 3.71 (m, 1H), 3.90 (br. s, 1H), 4.04 (d, *J* = 15.2 Hz, 1H), 5.07 (d, *J* = 15.2 Hz, 1H), 6.75 (br. s, 1H), 6.90 (m, 1H), 7.15-7.45 (m, 10H), 7.75 (m, 1H) ppm. Mass Spectrum: (ESI) m/z 566 $(M+H)^+$.

J: (*S*)-[1-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-ylmethyl]-isopropyl-carbamic acid tert-butyl ester. To a solution of

(*S*)-{1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-6-oxo-piperazin-2-ylmethyl}-isopropyl-carbamic acid tert-butyl ester (1 g, 1.77 mmol) in anhydrous CH_2Cl_2 (50 mL) at 0 °C was added triethylamine (0.37 mL, 2.66 mmol) followed by 6-chloro-benzo[b]thiophene-2-sulfonyl chloride (0.57 g, 2.12 mmol). The solution was stirred at 0 °C for 2 h and at ambient temperature for 1 h then partitioned between water (100 mL) and CH_2Cl_2 (100 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL) and the combined organic phases were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated to afford 1.41 g (100%) of (*S*)-[1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-ylmethyl]-isopropyl-carbamic acid tert-butyl ester as a yellow foam which was used without further purification. Mass Spectrum: (ESI) *m/z* 796 $(M+H)^+$.

The following compounds were prepared according to the above procedures, using the appropriate sulfonyl chlorides or aryl bromides.

Example	Name	m/z$(M+H)^+$
1477	(*S*)-[1-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-4-(5-chloro-1H-indole-2-sulfonyl)-6-oxo-piperazin-2-ylmethyl]-isopropyl-carbamic acid tert-butyl ester	879
1478	(*S*)-[1-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-4-(6-chloro-1H-indole-2-sulfonyl)-6-oxo-piperazin-2-ylmethyl]-isopropyl-carbamic acid tert-butyl ester	879
1479	(*S*)-[1-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-oxo-piperazin-2-ylmethyl]-isopropyl-carbamic acid tert-butyl ester	780
1480	(*S*)-[1-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-4-(5-chloro-1H-indol-2yl-methyl)-6-oxo-piperazin-2-ylmethyl]-isopropyl-carbamic acid tert-butyl ester	829
1481	(S)-{1-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl}-isopropyl-carbamic acid tert-butyl ester	763

Example 1482: (*S*)-[1-(3-Amino-4-cyano-benzyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-ylmethyl]-isopropyl-carbamic acid tert-butyl ester. To a solution of (*S*)-[1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-ylmethyl]-isopropyl-carbamic acid tert-butyl ester (1.41 g, 1.77 mmol) in a mixture of MeOH (20 mL) and THF (50 mL) at 0 °C was added conc. HCl (10 drops). The

mixture was stirred at 0 °C for 1 h then concentrated to dryness and flash column chromatographed on silica gel (CH_2Cl_2→1% MeOH / CH_2Cl_2→5%) to afford 1.11 g (100%) of (*S*)-[1-(3-amino-4-cyano-benzyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-ylmethyl]-isopropyl-carbamic acid tert-butyl ester as a yellow gum. Mass Spectrum: (ESI)*m/z* 632 $(M+H)^+$.

Example 1483: (*S*)-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-ylmethyl]-isopropyl-carbamic acid tert-butyl ester.

To a suspension of (*S*)-[1-(3-amino-4-cyano-benzyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-ylmethyl]-isopropyl-carbamic acid tert-butyl ester (1.11g, 1.77 mmol) in abs. EtOH (50 mL) were added 1,3,5-triazine (1.43 g, 17.7 mmol) and glacial acetic acid (1.01 mL, 17.7 mmol). The mixture was warmed to reflux (became homogeneous) and stirred for 16 h. The cooled mixture was concentrated to dryness and flash column chromatographed on silica gel (CH_2Cl_2→1% MeOH / CH_2Cl_2→2%→5%) to afford 0.8 g (68%) of (*S*)-[1-(4-amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-ylmethyl]-isopropyl-carbamic acid tert-butyl ester as a yellow foam. ^{1}H NMR (300 MHz, $CDCl_3$) ↗ 1.23 (t, *J* = 6.6 Hz, 6H), 1.45 (s, 9H), 2.80 (br. s, 1H), 3.30 (m, 1H), 3.85 (m, 3H), 4.28 (d,*J* = 16.7 Hz, 1H), 5.39 (d, *J* = 15.4 Hz, 1H), 7.45 (dd, *J* = 8.6, 1.9 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.84 (m, 3H), 8.40 (s, 1H) ppm. Mass Spectrum: (ESI) *m/z* 659 $(M+H)^+$.

Example 1484 (*S*)-1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isopropylaminomethyl)-piperazin-2-one.

To a solution of (*S*)-[1-(4-amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-ylmethyl]-isopropyl-carbamic acid tert-butyl ester (0.8 g, 1.22 mmol) in anhydrous CH_2Cl_2 at 0 °C was added trifluoroacetic acid (5 mL). The solution was stirred, capped for 16 h then concentrated to dryness and purified by reverse-phase HPLC on a 2" Dynamax C18 column (10→80% ACN / H_20 /0.1% TFA). Appropriate fractions were combined and lyophilized to afford 0.58 g (86%) of the TFA salt of (*S*)-1-(4-aminoquinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isopropyl aminomethyl)-piperazin-2-one as a white solid. ^{1}H NMR (300 MHz, DMSO-$_6$) ↗ 1.22 (dd, *J* = 6.5, 2.1 Hz, 6H), 3.22 (m, 3H), 3.72 (m, 3H), 4.01 (s, 1H), 4.07 (d, *J* = 15.6 Hz, 1H), 4.38 (d, *J* = 16.7 Hz, 1H), 5.12 (d, *J* = 16.7 Hz, 1H), 7.58 (s, 1H), 7.59 (s, 1H), 7.60 (dd, *J* = 8.6, 1.9 Hz, 1H), 8.09 (d, *J* = 8.6 Hz, 1H), 8.19 (s, 1H), 8.26 (d, *J* = 8.6 Hz, 1H), 8.36 (s, 1H), 8.50 (br. s, 1H), 8.72, (s, 1H), 9.49 (br. s, 2H) ppm. Mass Spectrum: (ESI) *m/z* 559 $(M+H)^+$.

The following compounds were prepared according to the above procedures:

Example 1485 (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-(isopropylamino-methyl)-piperazin-2-one.

^{1}HNMR (300 MHz, DMSO-d_6) ↗ 1.20 (d, *J* = 6.41 Hz, 6H), 3.45 (m, 5H), 3.76 (m, 1H), 3.93 (d, *J* = 16.5 Hz, 1H), 4.15 (m, 1H), 4.39 (d, *J* = 16.6 Hz, 1H), 5.12 (d, *J* = 16.6 Hz, 1H), 7.43 (d, *J* = 6.6 Hz, 1H), 7.56 (s, 2H), 7.79 (m, 2H), 8.28 (d, *J* = 8.59 Hz, 1H), 8.45 (m, 1H), 8.70 (s, 2H), 9.52 (br. S, 2H) ppm. Mass Spectrum: (ESI) *m/z* 542 (M^+).

Example 1486 (*S*)-1-(4-Aminoquinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-(isopropylamino-methyl)-piperazin-2-one.

^{1}H NMR (300 MHz, DMSO-d_6) ↗ 1.20 (m, 6H), 3.15 (m, 1H), 3.32 (m, 1H), 3.50 (m, 3H), 3.75 (m, 1H), 3.92 (d, *J* = 13.1 Hz, 1H), 4.10 (d, *J* = 16.3 Hz, 1H), 4.36 (d, *J* = 16.8 Hz, 1H), 5.12 (d, *J* = 16.8 Hz, 1H), 7.09 (s, 1H), 7.35 (dd, *J* = 9.1, 2.1 Hz, 1H), 7.54 (m, 3H), 7.80 (s, 1H), 8.26 (d, *J* = 8.6 Hz, 1H), 8.47 (m, 1H), 8.64 (m, 1H), 8.72 (br. s, 1H), 12.58 (s, 1H) ppm. Mass Spectrum: (ESI) *m/z* 542 $(M+H)^+$.

Example 1487 (*S*)-1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isopropylamino-methyl)-piperazin-2-one.

^{1}H NMR (300 MHz, DMSO-d_6) ↗ 1.20 (m, 6H), 3.38 (m, 5H), 3.72 (m, 1H), 3.90 (d, *J* = 13.0 Hz, 1H), 4.10 (d, *J* = 16.2 Hz, 1H), 4.36 (d, *J* = 16.2 Hz, 1H), 5.12 (d, *J* = 17.0 Hz, 1H), 7.20 (m, 2H), 7.51 (m, 3H), 7.75 (d, *J* = 8.6 Hz, 1H), 8.25 (d, *J* = 8.6 Hz, 1H), 8.45 (m, 1H), 8.59 (m, 1H), 8.71 (br. s, 1H), 12.53 (s, 1H) ppm. Mass Spectrum: (ESI) *m/z* 542 $(M+H)^+$.

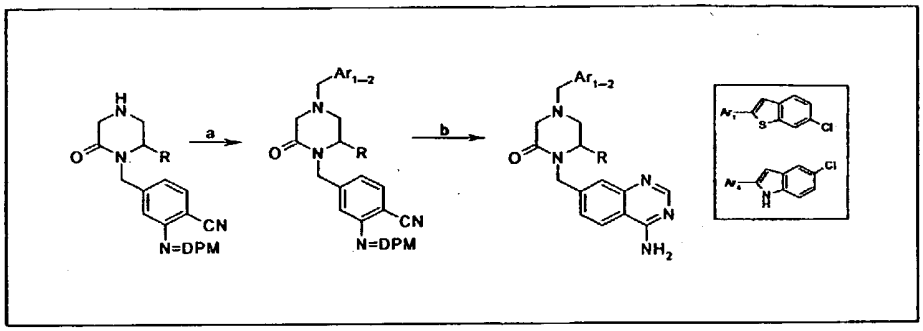
Example 1488 (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-(isopropylamino-methyl)-piperazin-2-one.

^{1}H NMR (500 MHz, DMSO-d_6) ↗ 1.15 (dd, *J* = 15.93, 6.59 Hz, 6H), 2.70 (dd, *J* = 12.63, 3.29 Hz, 1H), 3.06 ((m, 2H), 3.20 (d, *J* = 12.09 Hz, 1H), 3.28 (m, 1H), 3.47 (d, *J* = 17.20 Hz, 1H), 3.57 (m, 1H), 3.59 (m, 2H), 4.37 (d, *J* = 16.48 Hz, 1h), 5.15 (d, *J* = 16.48 Hz, 1H), 7.04 (dd, *J* = 8.51, 1.92 Hz, 1H), 7.33 (d, *J* = 8.79 Hz, 1H), 7.50 (d, *J* = 2.2 Hz, 1H), 7.55 (s, 1H), 7.60 (dd, *J* = 8.78, 1.10 Hz, 1H), 8.36 (d, *J* = 8.24 Hz, 3H), 8.78 (s, 1H), 9.70 (m, 2H) ppm. Mass Spectrum: (ESI) *m/z* 492 $(M+H)^+$.

Example 1489 (*S*)-1-(4-Aminoquinazolin-7-ylmethyl)-4-[5-(5-chlorothiophen-2-yl)isoxazol-3-ylmethyl]-6-(isopropylamino-methyl)-piperazin-2-one.

^{1}H NMR (600 MHz, DMSO-d_6) ↗ 1.23 (dd, J = 10.0, 6.50 Hz, 6H), 2.70 (d, J = 10.4 Hz, 1H), 3.20 (m, 3H), 3.40 (m, 1H), 3.60 (m, 3H), 3.84 (dd, J = 33.9, 14.5 Hz, 2H), 4.41 (d, J = 16.7 Hz, 1H), 5.21 (d, J = 16.7 Hz, 1H), 6.95 (s, 1H), 7.31 (d, J = 4.0 Hz, 1H), 7.62 (m, 3H), 8.40 (m, 3H), 8.85 (s, 1H), 9.81 (br. S, 1H) ppm. Mass Spectrum: (ESI) *m/z* 526 $(M+H)^+$.

Scheme 7 A synthetic scheme of the C(6)-alkylaminomethyl substituted alkyl inhibitors.



Reagents: (a) Aryl bromide, K_2CO_3, DMF. (b) 1. Conc. HCl, MeOH 2. Triazine, AcOH, EtOH, Reflux. (c) TFA, CH_2Cl_2.

Example 1490. (*S*)-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-yl]-acetic acid (RPR 257329A).

A: (*S*)-2-{4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-tert-butoxy carbonylmethyl-5-oxo-piperazin-1-ylmethyl}-5-chloro-indole-1-carboxylic acid tert-butyl ester. To a suspension of (*S*)-{1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-6-oxo-piperazin-2-yl}-acetic acid tert-butyl ester(265 mg, 0.52 mmol) and K_2CO_3 (133 mg, 0.96 mmol) in acetonitrile (1 mL) at 0°C was added 2-bromomethyl-5-chloro-indole-1-carboxylic acid tert-butyl ester (253 mg, 0.73 mmol). After warming to ambient temperature over 16 h the reaction was partitioned between EtOAc and water. The water was extracted with EtOAc and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated. Chromatography on SiO_2 (CH_2Cl_2 to 1% MeOH / CH_2Cl_2) afforded 300 mg (75%) of (*S*)-2-{4-[3-(benzhydrylidene-amino)-4-cyano]-3-tert-butoxy carbonylmethyl-5-oxo-piperazin-1-ylmethyl}-5-chloro-indole-1-carboxylic acid tert-butyl ester as a yellow glass. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, J = 9.0 Hz, 1H), 7.77 (d, J = 6.5 Hz, 2H), 7.38-7.47 (m, 4H), 7.23-7.29 (m, 4H), 7.17-7.21 (m, 3H), 6.84 (d J = 8.0 Hz, 1H), 6.66 (s, 1H), 6.48 (s, 1H), 5.05 (d, J = 15.5 Hz, 1H), 3.97 (d, J = 14.3 Hz, 1H), 3.78-3.89 (m, 2H), 3.58 (d, J = 16.3 Hz, 1H), 3.41-3.49 (m, 1H), 2.99 (d, J = 16.7 Hz, 1H), 2.71-2.87 (m, 2H), 2.29-2.42 (m, 2H), 1.67 (s, 9H), 1.26 (s, 9H) ppm. Mass Spectrum: (ESI)*m/z* 772 $(M+H)^+$.

B: (*S*)-2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-tert-butoxycarbonyl-5-oxo-piperazin-1-ylmethyl] -5-chloro-indole-1-carboxylic acid tert-butyl ester. To a solution of (*S*)-2-{4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-tert-butoxy carbonyl methyl-5-oxo-piperazin-1-ylmethyl}-5-chloro-indole-1-carboxylic acid tert-butyl ester (300 mg, 0.388 mmol) in a mixture of MeOH (10 mL) and THF (2 mL) at 0 °C was added conc. HCl (7 drops). After stirring for 1 h the reaction was stopped and flash column chromatographed on silica gel (CH_2Cl_2→8% MeOH / CH_2Cl_2) to afford 170 mg (72%) of (*S*)-2-[4-(3-amino-4-cyano-benzyl)-3-tert-butoxycarbonyl-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester as a yellow gum. Mass Spectrum: (ESI) *m/z* 608 $(M+H)^+$.

A solution of (*S*)-2-[4-(3-amino-4-cyano-benzyl)-3-tert-butoxycarbonyl-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester (170 mg, 0.28 mmol), glacial acetic acid (160 µL, 2.80 mmol) and 1,3,5-triazine (225 mg, 2.80 mmol) in absolute EtOH (4 mL) was heated to reflux for 16 h. The mixture was concentrated to dryness then flash column chromatographed on silica gel (CH_2Cl_2→8% MeOH / CH_2Cl_2) to afford 101 mg (58%) of (*S*)-2-[4-(4-amino-quinazolin-7-ylmethyl)-3-tert-butoxycarbonyl-5-oxo-piperazin-1-ylmethyl]-5-chloro -indole-1-carboxylic acid tert-butyl ester as an off-white glass. ^1H NMR (300 MHz, CD_3OD) δ 8.36 (s, 1H), 8.11 (d, *J* = 8.6 Hz, 1H), 7.97 (d, *J* = 9.0 Hz, 1H), 7.46-7.56 (m, 2H), 7.42 (d, *J* = 7.2 Hz, 1H), 7.22 (dd, *J* = 9.0, 2.2 Hz, 1H), 6.60 (s, 1H), 5.21 (d, *J* = 15.7 Hz, 1H), 4.34 (d, *J* = 15.6 Hz, 1H), 4.18 (d, *J* = 13.6 Hz, 1H), 3.58-3.73 (m, 2H), 3.17 (d, *J* = 16.8 Hz, 1H), 2.73-2.89 (m, 2H), 2.48-2.61 (m, 2H), 1.70 (s, 9H), 1.08 (s, 9H) ppm. Mass Spectrum: (ESI)*m/z* 635 $(M+H)^+$.

C: (*S*)-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-yl]-acetic acid (RPR 257329A). A solution of (*S*)-2-[4-(4-amino-quinazolin-7-ylmethyl)-3-tert-butoxycarbonyl-5-oxo-piperazin-1-ylmethyl]-5-chloro -indole-1-carboxylic acid tert-butyl ester (101 mg, 0.159 mmol) in CH_2Cl_2 (5 mL) and TFA (1 mL) was stirred for 16 h. The mixture was concentrated to dryness and the crude material was purified by RP-HPLC eluting with a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 80% CH_3CN/H_2O (0.1% TFA). The appropriate product fractions were combined and lyophilized to afford 34 mg (36%) of the TFA salt of (*S*)-[1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-yl]-acetic acid as a white solid. ^1H NMR (300 MHz, CD_3OD) ↗ 10.68 (s, 1H), 8.64 (s, 1H), 8.27 (d, *J* = 8.5 Hz, 1H), 7.66 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.57 (s, 1H), 7.43 (d, *J* = 2.0 Hz, 1H), 7.29 (d, *J* = 8.6 Hz, 1H), 7.02 (dd, *J* = 8.6, 2.0 Hz, 1H), 6.34 (s, 1H), 5.18 (d, *J* = 16.3 Hz, 1H), 4.51 (d, *J* = 16.3 Hz, 1H), 3.71-3.89 (m, 3H), 3.56 (d, *J* = 17.8 Hz, 1H), 3.02-3.17 (m, 3H), 2.61-2.75 (m, 2H) ppm. Mass Spectrum (ESI) *m/z* 479 $(M+H)^+$.

The following compounds were prepared according to the above procedure:

Example 1491 (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-isobutyl-piperazin-2-one.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.22 (s, 1H); 8.33 (s, 1H); 8.12 (d, *J* = 8.5 Hz, 1H); 7.72 (bs, 2H); 7.44 (d, *J* = 15.6 Hz, 1 H); 7.25-7.32 (m, 2H); 7.00 (dd, *J* = 8.6, 2.0 Hz, 1H); 6.29 (s, 1H); 5.05 (d , *J* = 15.4 Hz, 1H); 4.23 (d, *J* = 15.7 Hz, 1H); 3.81 (d, *J* = 13.3 Hz, 1H); 3.57 (d, *J* = 13.8 Hz, 1H); 3.40 (d, *J* = 16.2 Hz, 1H); 3.21-3.34 (m, 1H); 3.10-3.18 (m, 1H); 3.04 (d, *J* = 16.5 Hz, 1H); 2.66-2.74 (m, 1H); 2.31-2.39 (m, 1H); 1.22-1.30 (m, 1H); 1.06-1.19 (m, 1H); 0.70 (d, *J* = 6.5 Hz, 3H); 0.62 (d, *J* = 6.3 Hz, 3H) ppm. Mass Spectrum: (ESI) *m/z* 477 $(M+H)^+$.

Example 1492 (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-isobutyl-piperazin-2-one.

^{1}H NMR (DMSO-d_6) ↗ 11.30 (s, 1H), 9.74 (s, 2H), 8.79 (s, 1H), 8.34 (d, *J* = 8.6 Hz, 1H), 7.58 (m, 3H), 7.33 (d, *J* = 8.6 Hz, 1H), 7.03 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.35 (s, 1H), 5.02 (d, *J* = 16.5 Hz, 1H), 4.38 (d, *J* = 16.5 Hz, 1H), 3.95 (br d, 1H), 3.82 (d, 1H), 3.60 (d, 1H), 3.40 (d, 1H), 3.29 (br d, 1H), 2.82 (m, 1H), 2.60 (m, 1H), 1.90 (m, 1H), 1.29 (m, 2H), 0.71 (dd, *J* = 21.1, 6.0 Hz, 6H) ppm. Mass Spectrum (ESI) *m/z* 477 $(M+H)^+$.

Example 1493 (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-6-isobutyl-piperazin-2-one.

^{1}H NMR (300 MHz, CD_3OD) ↗ 8.65 (s, 1H), 8.29 (d, *J* = 8.6 Hz, 1H), 7.83 (d, *J* = 1.9 Hz, 1H), 7.70 (m, 2H), 7.58 (s, 1H), 7.30 (m, 2H), 5.11 (d, *J* = 16.4 Hz, 1H), 4.52 (d, *J* = 16.4 Hz, 1H), 4.02 (dd, *J* = 13.9, 0.86 Hz, 1H), 3.86 (d, *J* = 14.1 Hz, 1H), 3.63 (d, *J* = 16.7 Hz, 1H), 3.40 (m, 1H), 3.19 (d, *J* = 16.8 Hz, 1H), 3.0 (m, 1H), 2.60 (m, 1H), 2.08 (m, 1H), 1.32 (m, 2H), 0.80 (dd, *J* = 13.7, 5.9 Hz, 6H) ppm. Mass Spectrum: (ESI) *m/z* 494 $(M+H)^+$.

Example 1494 (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-6-isobutyl-piperazin-2-one.

^{1}H NMR (300 MHz, CD_3OD) ↗ 8.65 (s, 1H), 8.28 (d, *J* = 8.6 Hz, 1H), 7.84 (d, *J* = 1.8 Hz, 1H), 7.66 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.59 (s, 1H), 7.32 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.29 (s, 1H), 5.12 (d, *J* = 16.4 Hz, 1H), 4.53 (d, *J* = 16.4 Hz, 1H), 4.04 (d, *J* = 14.0 Hz, 1H), 3.88 (d, *J* = 14.0 Hz, 1H), 3.65 (d, *J* = 16.7 Hz, 1H), 3.40 (d, *J* = 9.3 Hz, 1H), 3.22 (d, *J* = 16.7 Hz, 1H), 3.00 (d, *J* = 12.1

Hz, 1H), 2.68 (m, 1H), 2.08 (m, 1H), 1.35 (m, 2H), 0.81 (dd,*J* = 23.0, 5.9 Hz, 6H) ppm. Mass Spectrum: (ESI) *m/z* 494 $(M+H)^+$.

Example 1494 (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-methoxymethyl-piperazin-2-one.

^{1}H NMR (DMSO-d_6) ↗ 11.31 (s, 1H), 9.75 (d, *J* = 5.5 Hz, 2H), 8.79 (s, 1H), 8.34 (d, *J* = 8.6 Hz, 1H), 7.55 (m, 3H), 7.06 (d, *J* = 1.9 Hz, 1H), 7.03 (d, *J* = 1.7 Hz, 1H), 6.38 (s, 1H), 4.96 (d, *J* = 16.6 Hz, 1H), 4.61 (d, *J* = 16.6 Hz, 1H), 3.88 (q, *J* = 13.9 Hz, 2H), 3.40-3.62 (m, 4H), 3.28 (m, 1H), 3.07 (s, 3H), 3.01 (m, 1H), 2.72 (m, 1H) ppm. Mass Spectrum: (ESI) *m/z* 465 $(M+H)^+$.

Example 1495 (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-methoxymethyl-piperazin-2-one.

^{1}H NMR (DMSO-d_6) ↗ 11.31 (s, 1H), 9.75 (d, *J* = 5.7 Hz, 1H), 8.79 (s, 1H), 8.34 (d, *J* = 8.6 Hz, 1H), 7.55 (m, 3H), 7.35 (d, *J* = 8.6 Hz, 1H), 7.04 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.38 (s, 1H), 4.95 (d, *J* = 16.6 Hz, 1H), 4.60 (d, *J* = 16.6 Hz, 1H), 3.88 (q, *J* = 13.9 Hz, 2H), 3.40-3.60 (m, 4H), 3.20 (m, 1H), 2.72 (m, 1H) ppm. Mass Spectrum: (ESI) *m/z* 465 $(M+H)^+$.

Example 1496 (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-6-methoxymethyl-piperazin-2-one.

^{1}H NMR (300 MHz, CD_3OD) ↗ 11.10 (s, 1H), 8.28 (d, *J* = 8.6 Hz, 1H), 7.86 (d, *J* = 1.9 Hz, 1H), 7.71 (d, *J* = 8.6 Hz, 1H), 7.65 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.58 (s, 1H), 7.32 (m, 2H), 5.07 (d,*J* = 16.4 Hz, 1H), 4.76 (d, *J* = 16.4 Hz, 1H), 3.97 (ABq, *J* = 32.9, 14.6 Hz, 2H), 3.55-3.70 (m, 4H), 3.19 (s, 3H), 3.10 (m, 2H), 2.72 (m, 1H) ppm. Mass Spectrum: (ESI) *m/z* 481 M^+.

Example 1497 (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-6-methoxymethyl-piperazin-2-one

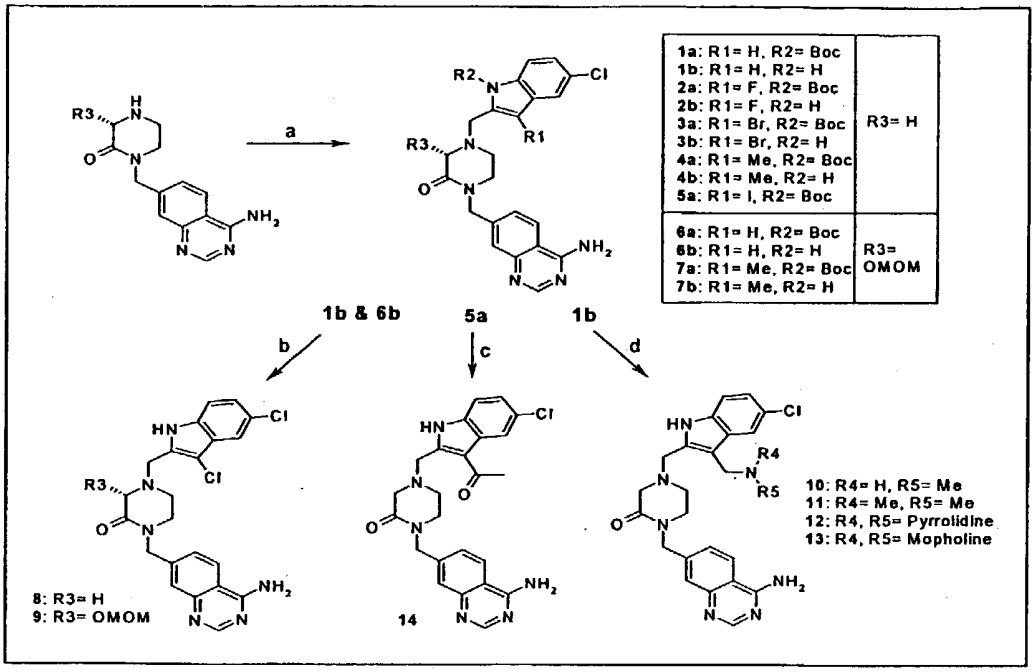
^{1}H NMR (300 MHz, CD_3OD) ↗ 8.65 (s, 1H), 8.28 (d, *J* = 8.6 Hz, 1H), 7.86 (d, *J* = 1.9 Hz, 1H), 7.71 (d, *J* = 8.6 Hz, 1H), 7.65 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.58 (s, 1H), 7.32 (m, 2H), 5.07 (d,*J* = 16.5 Hz, 1H), 4.76 (d, *J* = 16.5 Hz, 1H), 3.99 (ABq, *J* = 33.0, 14.1 Hz, 2H), 3.58-3.70 (m, 4H), 3.19 (s, 3H), 3.15 (m, 2H), 2.76 (m, 1H) ppm. Mass Spectrum: (ESI) *m/z* 482 $(M+H)^+$.

Example 1498 (*R/S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid.

^{1}H NMR (300 MHz, CD_3OD) δ 8.63 (s, 1H), 8.25 (d, *J* = 8.6 Hz, 1H), 7.64 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.57 (s, 1H), 7.43 (d, *J* = 1.9 Hz, 1H), 7.26 (d, *J* = 8.6, 1H), 7.01 (dd, *J* = 8.6, 2.0 Hz, 1H),

6.32 (s, 1H), 5.38 (d, J = 16.4 Hz, 1H), 4.28 (d, J = 16.4 Hz, 1H), 4.17-4.22 (m, 1H), 3.68-3.89 (m, 2H), 3.58 (d, J = 16.9 Hz, 1H), 3.47 (d, J = 12.0 Hz, 1H), 3.16 (d, J = 16.7 Hz, 1H), 2.73-2.80 (m, 1H) ppm. Mass Spectrum: (ESI) m/z 465 $(M+H)^+$.

Scheme 8 A synthetic scheme of the C(3')- substituted indolylmethyl inhibitors.



Reagents: (a). 1. $ArCH_2Br$, K_2CO_3, DMF 2. (a->b) TFA, CH_2Cl_2 (b). NCS (c). 1. $Pd(PPh_3)_4$, CuI, TEA, TMSCCH, DMF 2. K2CO3 (d). Amine, formaldehyde, dioxane/AcOH.

Example 1499. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one

A: 2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester. To a solution of 1-(4-Amino-quinazolin-7-ylmethyl)-piperazin-2-one (500 mg, 1.94 mmol) in DMSO (15 mL) was added K_2CO_3 (423 mg, 3.01 mmol) followed by 2-bromomethyl-5-chloro-indole-1-carboxylic acid tert-butyl ester (744 mg, 2.16 mmol). After stirring for 16 h the reaction was partitioned between water and EtOAc. The EtOAc was washed with water, then brine, dried over Na_2SO_4, filtered, and concentrated. Chromatography on SiO_2 (CH_2Cl_2 to 8% MeOH / CH_2Cl_2) afforded 924 mg (92%) of 2-[4-(4-amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester as a pale crunchy solid. ^1H NMR (300 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.92 (d, J = 8.9 Hz, 1H), 7.76 (d, J = 8.5 Hz, 1H), 7.67 (d, J = 1.0 Hz, 1H), 7.40-7.47 (m, 2H), 7.19 (dd, J = 8.9, 2.1 Hz, 1H), 6.50 (s,

1H), 5.87 (br s, 2H), 4.75 (s, 2H), 3.94 (s, 2H), 3.37 (s, 2H), 3.30 (t,*J* = 4.9 Hz, 2H), 2.77 (t, *J* = 5.6 Hz, 2H), 1.64 (s, 9H) ppm.

B: 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one (RPR 210312A). To a solution of 2-[4-(4-amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester (400 mg, 0.76 mmol) in CH_2Cl_2 (10 mL) was added TFA (2 mL). After stirring for 16 h, chromatography on SiO_2 (CH_2Cl_2 to 20% MeOH / CH_2Cl_2) afforded 393 mg (>100%) of 1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one as an off white solid. ^{1}H NMR (300 MHz, DMSO-d_6) ↗ 11□□ □s, □□), 9.64 (br s, 2H), 8.77 (s, 1H), 8.35 (d, *J* = 8.5 Hz, 1H), 7.53-7.62 (m, 2H), 7.49 (d, *J* = 2.0 Hz, 1H), 7.31 (d, *J* = 8.6 Hz, 1H), 7.02 (dd, *J* = 8.6, 2.0 Hz, 1H), 6.33 (s, 1H), 4.70 (s, 2H), 3.78 (s, 2H), 3.26-3.34 (m, 2H), 3.22 (s, 2H), 2.76 (s, 2H) ppm.

Example 1500 1-(4-Amino-quinazolin-7-ylmethyl)-4-(3,5-dichloro-1H-indol-2-ylmethyl)-piperazin-2-one

A solution of 1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one (115 mg, 0.273 mmol) in MeOH (3 mL) was treated with NCS (35 mg, 0.262 mmol) and stirred for 90 min. The crude material was purified by RP-HPLC eluting with a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 60% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions were combined and lyophilized to afford 55 mg (41%) of the TFA salt of 1-(4-amino-quinazolin-7-ylmethyl)-4-(3,5-dichloro-1H-indol-2-ylmethyl)-piperazin-2-one as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) ↗ 11□□ (s, 1H), 9.73 (br s, 2H), 8.79 (s, 1H), 8.35 (d, *J* = 8.4 Hz, 1H), 7.59 (d, *J* = 8.7 Hz, 1H), 7.55 (s, 1H), 7.45-7.45 (m, 2H), 7.15 (dd,*J* = 8.6, 2.0 Hz, 1H), 4.70 (s, 2H), 4.44 (s, 2H), 3.82 (s, 2H), 3.32 (br s, 4H) ppm. Mass Spectrum: (ESI)*m/z* 455 $(M+H)^+$.

Example 1501 4-(3-Acetyl-5-chloro-1H-indol-2-ylmethyl)-1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one

A: 2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-5-chloro-3-trimethylsilanyl ethynyl-indole-1-carboxylic acid tert-butyl ester.

To a mixture of 2-[4-(4-amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-5-chloro-3-iodo-indole-1-carboxylic acid tert-butyl ester (190 mg, 0.29 mmol), copper(I) iodide (10 mg, 0.046 mmol), and *bis*(triphenylphosphine)-palladium dichloride (12 mg, 0.17 mmol) in Et_3N (1.5 mL) and DMF (0.5 mL) was added (trimethylsilyl)acetylene (100 μL, 0.70 mmol). After stirring for 16 h the reaction was partitioned between water and EtOAc. The aqueous phase was

extracted with EtOAc and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Chromatography on SiO_2 (CH_2Cl_2 to 8% MeOH / CH_2Cl_2) afforded 133 mg (74%) of 2-[4-(4-amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-5-chloro-3-trimethylsilanyl ethynyl-indole-1-carboxylic acid tert-butyl ester as a brown solid. Mass Spectrum: (ESI) m/z 617 $(M+H)^+$.

B: 4-(3-Acetyl-5-chloro-1H-indol-2-ylmethyl)-1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one. To a solution of 2-[4-(4-amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-5-chloro-3-trimethylsilanylethynyl-indole-1-carboxylic acid tert-butyl ester (133 mg, 0.215 mmol) in MeOH (5 mL) was added K_2CO_3 (513 mg, 3.71 mmol). After stirring for 6 h the reaction was diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by RP-HPLC eluting with a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 50% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions were combined and lyophilized to afford 22 mg (15%) of the TFA salt of 4-(3-acetyl-5-chloro-1H-indol-2-ylmethyl)-1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one as a white solid. ^1H NMR (300 MHz, CD_3OD) δ 8□□□ □s, 1H), 8.31 (d, J = 8.5 Hz, 1H), 8.01 (d, J = 1.9 Hz, 1H), 7.69 (dd, J = 8.5, 1.5 Hz, 1H), 7.65 (s, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.21 (dd, J = 8.7, 2.0 Hz, 1H), 4.27 (s, 2H), 3.47-3.54 (m, 6H), 3.01-3.06 (m, 2H), 2.68 (s, 3H) ppm. Mass Spectrum: (ESI) *m/z* 463 $(M+H)^+$.

Example 1502 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-3-pyrrolidin-1-ylmethyl-1H-indol-2-ylmethyl)-piperazin-2-one

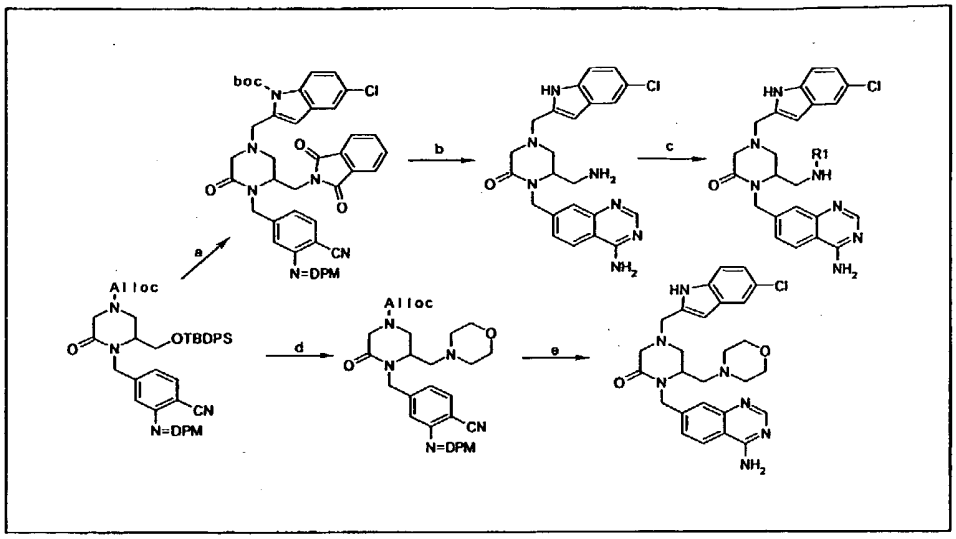
To a solution of formaldehyde (40 mg, 0.47 mmol) in a mixture of HOAc (1 mL) and dioxane (4 mL) at 0 °C was added pyrrolidine (36 μL, 0.43 mmol). After stirring for 5 min 1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one (107 mg, 0.254 mmol) was added in one portion. The reaction was allowed to warm to ambient temperature and after stirring for 2.5 h was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc. The organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by RP-HPLC eluting with a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 60% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions were combined and lyophilized to afford 70 mg (47%) of the TFA salt of 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-3-pyrrolidin-1-ylmethyl-1H-indol-2-ylmethyl)-piperazin-2-one as a white solid. ^1H NMR (300 MHz, DMSO-d_6) δ 11□□ (s, 1H), 9.78 (d, J = 1.7 Hz, 2H), 8.79 (s, 1H), 8.39 (d, J = 8.5 Hz, 1H), 7.87 (d, J = 1.5 Hz, 1H), 7.56-7.64 (m, 2H), 7.38 (d, J = 8.6 Hz, 1H), 7.12

(dd, J = 8.6, 1.8 Hz, 1H), 4.71 (s, 2H), 4.54 (s, 2H), 3.95 (s, 2H), 3.29 (s, 6H), 3.12 (br s, 2H), 2.82 (s, 2H, 1.95 (br s, 2H), 1.83 (br s, 2H) ppm. Mass Spectrum: (ESI) *m/z* 504 $(M+H)^+$.

The following compounds were prepared using appropriate indole precursors as described in above examples:

Example	Compound Name	m/z (M+H)
1503	(*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-bromo-5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one	499
1504	(*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-3-methyl-1H-indol-2-ylmethyl)-piperazin-2-one	434
1505	(*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-3-morpholin-4-ylmethyl-1H-indol-2-ylmethyl)-piperazin-2-one	520
1506	(*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-3-methylaminomethyl-1H-indol-2-ylmethyl)-piperazin-2-one	463
1507	(*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-3-dimethylaminomethyl-1H-indol-2-ylmethyl)-piperazin-2-one	477
1508	(*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-3-methyl-1H-indol-2-ylmethyl)-3-methoxymethyl-piperazin-2-one	478
1509	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-3-fluoro-1H-indol-2-ylmethyl)-piperazin-2-one	438
1510	(*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(3,5-dichloro-1H-indol-2-ylmethyl)-3-methoxymethyl-piperazin-2-one	499

Scheme 9 A synthetic scheme of the C(6)-alkylaminomethyl substituted indolylmethyl inhibitors.



Reagents: (a) 1. $Pd(PPh_3)_4$, morpholine, CH_2Cl_2. 2. K_2CO_3, 2-bromomethyl-5-chloro-indole-1-carboxylic acid tert butyl ester, DMF. 3. TBAF, THF. 4. Phthalimide, PPh_3, DEAD, THF. (b) 1. c-HCl, MeOH. 2. 1,3,5-Triazine, AcOH, EtOH, reflux. 3. TFA, CH_2Cl_2. 4. Hydrazine, EtOH. (c) Et_3N, electrophiles, CH_2Cl_2. (d) 1. TBAF, THF. 2. SO_3-Py, DMSO. 3. Amine, $NaB(OAc)_3H$, 4A MS, MeOH. (e) see (a.1-2), (b.1-2,4).

Example 1511 (*S*)-6-Aminomethyl-1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one

A: (*R*)-2-(benzhydrylidene-amino)-4-[2-(tert-butyl-diphenyl-silanyloxymethyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile.

Tetrakis(triphenylphosphine)palladium (470 mg, 0.38 mmol) was added to a solution of (*R*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-(tert-butyl-diphenyl-silanyloxy-methyl)-5-oxo-piperazine-1-carboxylic acid allyl ester (2.8 g, 3.8 mmol) and morpholine (1.7 mg, 19 mmol) in CH_2Cl_2 (30 mL). After 30 min at ambient temperature, the reaction mixture was concentrated and chromatographed on SiO_2 (1% CH_2Cl_2 to 5% MeOH in CH_2Cl_2) to provide 2.6 g (100%) of (*R*)-2-(benzhydrylidene-amino)-4-[2-(tert-butyl-diphenyl-silanyloxymethyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile as an oil. Mass Spectrum: (ESI) *m/z* 677 $(M+H)^+$.

B: (*R*)-2-[4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-(tert-butyl-diphenyl-silanyloxymethyl)-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester.

To a mixture of (*R*)-2-(benzhydrylidene-amino)-4-[2-(tert-butyl-diphenyl-silanyloxymethyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile (1.08 g, 1.6 mmol) and K_2CO_3 (0.66 g, 4.8 mmol) in DMF (3 mL) at 0 °C was added 2-bromomethyl-5-chloro-indole-1-carboxylic acid tert butyl ester (0.67 g, 1.95 mmol). After 1 h at ambient temperature, the reaction mixture was diluted with EtOAc

and water, and extracted with EtOAc. The combined organic extracts were washed twice with water and brine, dried ($MgSO_4$), filtered, and concentrated to afford crude (*R*)-2-[4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-(tert-butyl-diphenyl-silanyloxymethyl)-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester which was used in the next reaction without further purification. Mass Spectrum: (ESI) *m/z* 940 $(M+H)^+$.

C: (*R*)-2-{4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-hydroxymethyl-5-oxo-piperazin-1-ylmethyl}-5-chloro-indole-1-carboxylic acid tert-butyl ester. A solution of (*R*)-2-[4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-(tert-butyl-diphenyl-silanyloxymethyl)-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester in THF (20 mL) was treated with a 1.0 M solution of TBAF in THF (5 mL, 5 mmol). The reaction mixture was stirred for 1 h at ambient temperature, diluted with brine and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$), filtered, concentrated and chromatographed on SiO_2 (1% CH_2Cl_2 to 5% MeOH in CH_2Cl_2) to yield 2.46 g (94%) of (*R*)-2-{4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-hydroxymethyl-5-oxo-piperazin-1-ylmethyl}-5-chloro-indole-1-carboxylic acid tert-butyl ester. Mass Spectrum: (ESI) *m/z* 688 $(M+H)^+$.

D: (*R*)-2-[4-[3-(Benzhydrylidene-amino)-4-cyanobenzyl]-3-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester. In a 100 mL flask were placed (*R*)-2-{4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-hydroxymethyl-5-oxo-piperazin-1-ylmethyl}-5-chloro-indole-1-carboxylic acid tert-butyl ester (0.22 g, 0.32 mmol), triphenylphosphine (0.25 g, 0.96 mmol) and phthalimide (0.19 g, 1.28 mmol). Toluene (2 mL) and THF (2 mL) were added and the suspension was treated with DEAD (0.15 mL, 0.96 mmol) at -50 °C. The reaction mixture was allowed to warm to ambient temperature and was stirred for 48 h. The solution was concentrated and chromatographed on SiO_2 (hexanes/EtOAc, 5:1 to 1:1) to provide 240 mg (93%) of (*R*)-2-[4-[3-(benzhydrylidene-amino)-4-cyanobenzyl]-3-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester. Mass Spectrum: (ESI) *m/z* 817 $(M+H)^+$.

E: (*R*)-2-[4-(3-Amino-4-cyano-benzyl)-3-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester. Concentrated HCl (12M, 5 drops) was added to a solution of (*R*)-2-[4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester (0.24 g, 0.3 mmol) in MeOH (5 mL) at 0 °C. After 2 h at 0 °C, the

reaction mixture was concentrated and partitioned between EtOAc and saturated $NaHCO_3$ solution. The separated organic phase was washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude residue was chromatographed on silica gel (hexanes/EtOAc, 3:1 to 1:1) to afford 0.13 g (67%) of (*R*)-2-[4-(3-amino-4-cyano-benzyl)-3-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-5-oxo-piperazin -1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester. Mass Spectrum: (ESI) *m/z* 653 $(M+H)^+$.

F: (*R*)-2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester. To a solution of (*R*)-2-[4-(3-amino-4-cyano-benzyl)-3-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester (130 mg, 0.2 mmol) in absolute ethanol (7 mL) was added 1,3,5-triazine (162 mg, 2 mmol) and acetic acid (0.11 mL, 2 mmol). After the solution was heated to a reflux for 20 h, the solution was cooled and concentrated. The resulting crude product was chromatographed on SiO_2 (1% CH_2Cl_2 to 10% MeOH in CH_2Cl_2) to provide 100 mg (74%) of (*R*)-2-[4-(4-amino-quinazolin-7-ylmethyl)-3-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester. Mass Spectrum: (ESI) *m/z* 679 $(M+H)^+$.

G: (*R*)-2-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-isoindole-1,3-dione. Excess TFA (~30% in CH_2Cl_2) was added to a solution of (*R*)-2-[4-(4-amino-quinazolin-7-ylmethyl)-3-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester (100 mg, 0.15 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After 3 h at ambient temperature, the reaction mixture was concentrated to give the crude residue which was chromatographed on SiO_2 (2% CH_2Cl_2 to 20% MeOH in CH_2Cl_2) to afford 90 mg (100%) of (*R*)-2-[1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-isoindole-1,3-dione. Mass Spectrum: (ESI) *m/z* 580 $(M+H)^+$.

H: (*S*)-6-Aminomethyl-1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one (RPR257001A). A mixture of (*R*)-2-[1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-isoindole-1,3-dione (1.0 g, 1.5 mmol) in MeOH (30 mL) was treated with hydrazine monohydrate (30 mL, 75 mmol). After 12 h at ambient temperature, the reaction mixture was concentrated and dissolved in 0.1% TFA-containing acetonitrile and water, making 40 mL solution for a prep HPLC injection. The crude material was purified by RP-HPLC eluting with a gradient of 10% CH_3CN/H_2O (0.1% TFA) to

80% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions were combined and lyophilized to afford 0.91 g (89%) of (*S*)-6-aminomethyl-1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one as a white solid. Mass Spectrum: (ESI) *m/z* 450 $(M+H)^+$.

Example 1512 (*S*)-N-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-acetamide

To a solution of (*S*)-6-aminomethyl-1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one (15 mg, 0.022 mmol) and excess Et_3N in DMF (0.5 mL) was added acetic anhydride (0.008 mL) at 0 °C. After 1 h at ambient temperature, the reaction mixture was diluted with water and acetonitrile to make 10 mL of the solution. The crude material was purified by RP-HPLC eluting with a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 80% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions were combined and lyophilized to afford 11 mg (82%) of (*S*)-N-[1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-acetamide as a white solid. Mass Spectrum: (ESI) *m/z* 492 $(M+H)^+$.

The following compounds were prepared by the coupling reactions of the C(6)-aminomethyl templates with appropriate electrophiles as described in above examples.

Example	Compound Name	*m/z* (M+H)
1513	(*S*)-Furan-2-carboxylic acid [1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-amide	544
1514	(*S*)-N-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-formamide	477
1515	(*S*)-1-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-3-ethyl-urea	521
1516	(*S*)-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-urea	492
1517	(*S*)-5-Bromo-thiophene-2-sulfonic acid [1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-amide	675
1518	(*S*)-1-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-3-phenyl-urea	569
1519	(*S*)-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-	536

	6-oxo-piperazin-2-ylmethyl]-carbamic acid isopropyl ester	
1520	(*S*)-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-carbamic acid methyl ester	507
1521	(*S*)-N-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-methanesulfonamide	528

Example 1522 (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-morpholin-4-ylmethyl-piperazin-2-one

A: (*R*)-4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-formyl-5-oxo-piperazine-1-carboxylic acid allyl ester. A solution of (*R*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-hydroxymethyl-5-oxo-piperazine-1-carboxylic acid allyl ester (2.4 g, 4.7 mmol) in DMSO (8 mL) and Et_3N (4 mL) at 0 °C was treated with SO_3.Py (3.76 g, 24 mmol). After 20 h at ambient temperature, the mixture was diluted with water, and extracted with EtOAc. The combined organic extracts were washed with saturated NH_4Cl solution and water, dried ($MgSO_4$), concentrated. The crude (*R*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-formyl-5-oxo-piperazine-1-carboxylic acid allyl ester (~2.3 g) was used for next reactions without further purification. Mass Spectrum: (ESI) *m/z* 507 $(M+H)^+$.

B: (*S*)-4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-morpholin-4-ylmethyl-5-oxo-piperazine-1-carboxylic acid allyl ester. To a mixture of (*R*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-formyl-5-oxo-piperazine-1-carboxylic acid allyl ester (0.25 g, 0.49 mmol), morpholine (0.21 mL, 2.5 mmol) and powdered 4Å MS (0.5 g) in 1,2-dichloroethane (5 mL) was added sodium triacetoxy-borohydride (0.31 g, 1.5 mmol) at 0 °C. After 12 h at ambient temperature, the reaction mixture was quenched with saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was chromatographed on SiO_2 (2% CH_2Cl_2 to 5% MeOH in CH_2Cl_2) to afford 210 mg (73%) of (*S*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-morpholin-4-ylmethyl-5-oxo-piperazine-1-carboxylic acid allyl ester. Mass Spectrum: (ESI) *m/z* 578 $(M+H)^+$.

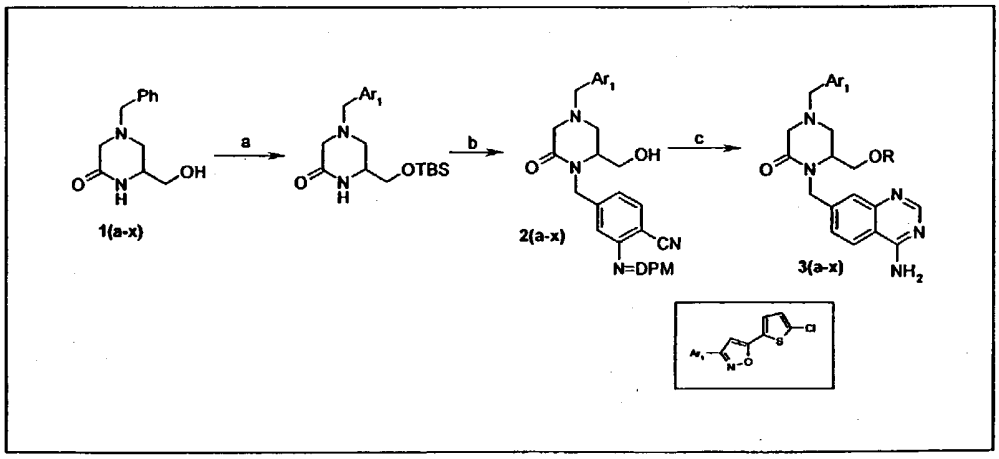
C: (*S*)-4-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-3-morpholin-4-ylmethyl-5-oxo-piperazine-1-carboxylic acid. Alloc deprotection of (*S*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-morpholin-4-ylmethyl-5-oxo-piperazine-1-carboxylic acid allyl ester was carried out as described in previous examples using *tetrakis*(triphenylphosphine)palladium and morpholine, to

afford (*S*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-morpholin-4-ylmethyl-5-oxo-piperazine-1-carboxylic acid in 100% yield. Mass Spectrum: (ESI) *m/z* 494 $(M+H)^+$.

D: (*S*)-2-[4-(3-Amino-4-cyano-benzyl)-3-morpholin-4-ylmethyl-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester. Coupling of (*S*)-4-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-3-morpholin-4-ylmethyl-5-oxo-piperazine-1-carboxylic acid allyl ester with 2-bromomethyl-5-chloro-indole-1-carboxylic acid tert butyl ester and deprotection of the diphenyl methylene group by HCl/MeOH were performed as described in previous examples to provide (*S*)-2-[4-(3-amino-4-cyano-benzyl)-3-morpholin-4-ylmethyl-5-oxo-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester in 43% yield. Mass Spectrum: (ESI) *m/z* 593 $(M+H)^+$.

E: (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-morpholin-4-ylmethyl-piperazin-2-one (RPR256996A). The aminoquinazoline formation and the subsequent Boc deprotection were carried out as described in previous examples to afford (*S*)-1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-morpholin-4-ylmethyl-piperazin-2-one. Mass Spectrum: (ESI) *m/z* 520 $(M+H)^+$.

Scheme 10 A synthetic scheme of the C(6)-alkoxymethyl substituted isoxazolylmethyl inhibitors.



Reagents: (a). 1. TBSCl, Imidazole. 2. $Pd(OH)_2$, MeOH, H_2. 3. NaH, Ar1CH_2Br, THF. (b). 1. NaH, 4-bromomethyl-2-diphenylmethyleneaminobenzonitrile, THF. 2. TBAF, THF. (c). 1. NaH, RBr, THF. 2. c-HCl, MeOH. 3. 1,3,5-Triazine, AcOH, EtOH, reflux.

Example 1523 (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-methoxymethyl-piperazin-2-one

A: (*R*)-4-Benzyl-6-(tert-butyl-dimethyl-silanyloxymethyl)-piperazin-2-one. A solution of (*R*)-4-benzyl-6-hydroxymethyl-piperazin-2-one (9 g, 41 mmol) and imidazole (4.2 g, 62 mmol) in CH_2Cl_2 (80 mL) at 0 °C was treated with TBSCl (6.24 g, 42 mmol). After 1 h at ambient temperature, the mixture was concentrated, diluted with EtOAc, and filtered to remove most of the triethylamine hydrochloride. Concentration of the solution provided 12.8 g (93%) of the crude (*R*)-4-benzyl-6-(tert-butyl-dimethyl-silanyloxymethyl)-piperazin-2-one which was used for the next reaction without further purification. Mass Spectrum: (ESI) *m/z* 335 $(M+H)^+$.

B: (*R*)-6-(tert-Butyl-dimethyl-silanyloxymethyl)-piperazin-2-one. To a solution of (*R*)-4-benzyl-6-(tert-butyl-dimethyl-silanyloxymethyl)-piperazin-2-one (2.1 g, 6.3 mmol) in MeOH (80 mL) was added 10% palladium hydroxide on C (0.3 g). The reaction mixture was hydrogenated at ambient temperature under a balloon of H_2 for 20 h. The reaction mixture was filtered through a pad of celite, and the filtrate was concentrated to afford 1.36 g (88%) of (*R*)-6-(tert-butyl-dimethyl-silanyloxymethyl)-piperazin-2-one. Mass Spectrum (ESI) *m/z* 245 $(M+H)^+$.

C: (*R*)-6-(tert-Butyl-dimethyl-silanyloxymethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-piperazin-2-one. To a mixture of (*R*)-6-(tert-butyl-dimethyl-silanyloxymethyl)-piperazin-2-one (1.36 g, 5.6 mmol) and K_2CO_3 (3.1 g, 22 mmol) in anhydrous DMF (10 mL) at 0 °C was added 3-bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole (1.72 g, 6.2 mmol). After 2 h at ambient temperature, the reaction mixture was diluted with EtOAc and water, and the layers were separated. The organic phase was washed twice with water, brine, dried ($MgSO_4$), filtered and concentrated. The crude residue was chromatographed on SiO_2 (CH_2Cl_2 to 10% MeOH in CH_2Cl_2) to provide 2.55 g (100%) of (*R*)-6-(tert-butyl-dimethyl-silanyloxymethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-piperazin-2-one. ^1H NMR (300 MHz, $CDCl_3$) δ □□27 (d, *J* = 4.2 Hz, 1H), 6.95 (d, *J* = 4.2 Hz, 1H), 6.35 (s, 1H), 6.09 (s, 1H), 3.7-3.45 (m, 5H), 3.33 (d, *J* = 16 Hz, 1H), 3.14 (d, *J* = 16 Hz, 1H), 2.76 (dd, *J* = 15, 3.6 Hz, 1H), 2.4-2.33 (m, 1H), 0.87 (s, 9H), 0.05 (s, 6H) ppm. Mass Spectrum: (ESI) *m/z* 442 $(M+H)^+$.

D: (*R*)-2-(Benzhydrylidene-amino)-4-{2-(tert-butyl-dimethyl-silanyloxymethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-1-ylmethyl}-benzonitrile. To a solution of (*R*)-6-(tert-butyl-dimethyl-silanyloxymethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-piperazin-2-one (2.55 g, 5.7 mmol) in a mixture of 5:1 THF:DMF (25 mL) at 0 °C was added NaH (a 60% dispersion in mineral oil, 0.32 g, 8 mmol) followed by 2-(benzhydrylidene-amino)-4-bromomethyl-benzonitrile (2.35 g, 6.3 mmol). After 0.5 h at 0°C, the reaction mixture was diluted with saturated NH_4Cl, and extracted with EtOAc. The combined organic extracts

were washed with water (twice), dried ($MgSO_4$), filtered and concentrated. The crude (*R*)-2-(benzhydrylidene-amino)-4-{2-(tert-butyl-dimethyl-silanyloxymethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-1-ylmethyl}-benzonitrile was used directly in the next reaction without further purification.

E: (*R*)-2-(Benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-hydroxymethyl-6-oxo-piperazin-1-ylmethyl}-benzonitrile. A solution of (*R*)-2-(benzhydrylidene-amino)-4-{2-(tert-butyl-dimethyl-silanyloxymethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-1-ylmethyl}-benzonitrile in THF (30 mL) was treated with a 1.0 M solution of TBAF in THF (7 mL, 7 mmol). The reaction mixture was stirred for 0.5 h at ambient temperature, concentrated and chromatographed on SiO_2 (CH_2Cl_2 to 4% MeOH in CH_2Cl_2) to yield 3.3 g (95%) of (*R*)-2-(benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-hydroxymethyl-6-oxo-piperazin-1-ylmethyl}-benzonitrile. ^{1}H NMR (300 MHz, $CDCl_3$) δ □□79 (d, *J* = 7.2 Hz, 2H), 7.6-7.2 (m, 10 H), 6.95 (d, *J* = 4.1 Hz, 1H), 6.90 (d, *J* = 6.9 Hz, 1H), 6.62 (s, 1H), 6.31 (s, 1H), 5.15 (d, *J* = 15.4 Hz, 1H), 3.96 (d, *J* = 15.4 Hz, 1H), 3.75-3.6 (m, 5H), 3.2-2.9 (m, 3H), 2.51 (dd, *J* = 11.7, 2.8 Hz, 1H) ppm. Mass Spectrum: (ESI) *m/z* 622 $(M+H)^+$.

F: (*R*)-2-(Benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl}-benzonitrile. To a solution of (*R*)-2-(benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-hydroxymethyl-6-oxo-piperazin-1-ylmethyl}-benzonitrile (0.15 g, 0.24 mmol) in THF/DMF (5:1, 6 mL) at 0 °C were added 60% NaH in mineral oil (26 mg, 0.68 mmol), followed, after 15 min, by the addition of MeI (0.018 mL, 0.29 mmol). After 1 h at ambient temperature, the mixture was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The crude (*R*)-2-(benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl}-benzonitrile was used directly in the next reaction without further purification.

G: (*R*)-2-Amino-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl}-benzonitrile. Concentrated HCl (12M, 5 drops) was added at 0 °C to a solution of (*R*)-2-(benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl}-benzonitrile in MeOH (5 mL). After 1 h at ambient temperature, the reaction mixture was concentrated and partitioned between EtOAc and saturated $NaHCO_3$ solution. The separated organic phase was washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude residue was chromatographed on silica gel

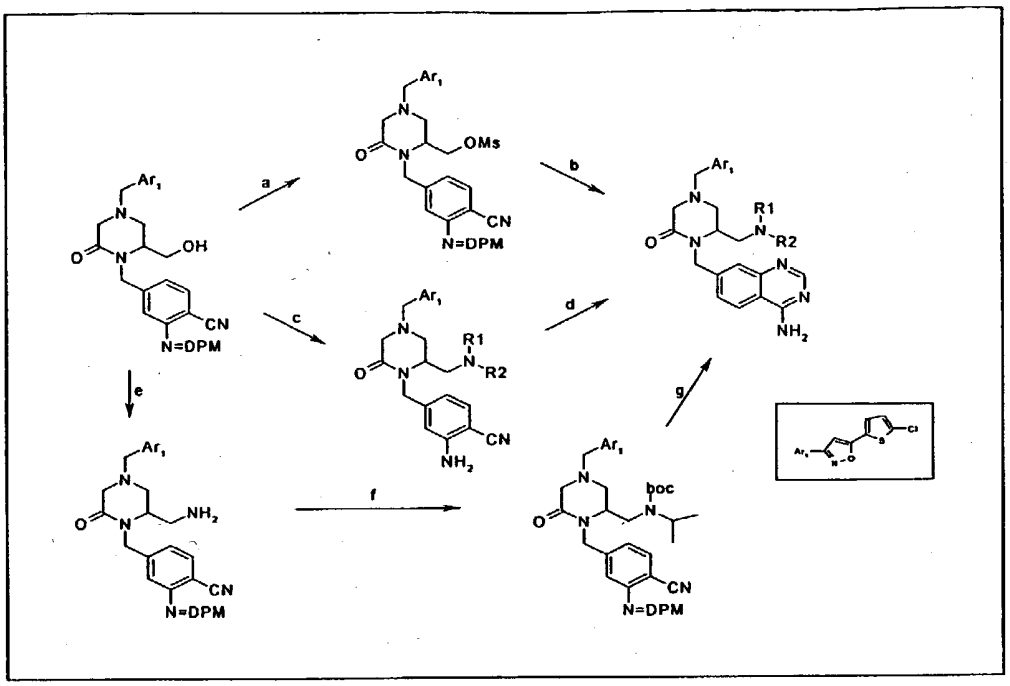
(CH_2Cl_2 to 5% MeOH in CH_2Cl_2) to provide 90 mg (79%) of (*R*)-2-amino-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl}-benzonitrile. Mass Spectrum: (ESI) *m/z* 472 $(M+H)^+$.

H: (*R*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-methoxymethyl-piperazin-2-one (RPR257852A). To a solution of (*R*)-2-amino-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl}-benzonitrile (90 mg, 0.19 mmol) in absolute ethanol (3 mL) was added 1,3,5-triazine (0.16 g, 1.9 mmol) and acetic acid (0.11 mL, 1.9 mmol). The solution was heated to reflux. After 15 h, the solution was concentrated and diluted with water and acetonitrile to make 10 mL of solution. The crude material was purified by RP-HPLC eluting with a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 80% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions were combined and lyophilized to give 75 mg (79%) of (*R*)-1-(4-amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-methoxymethyl-piperazin-2-one as a white solid. Mass Spectrum: (ESI) *m/z* 499 $(M+H)^+$.

The following compounds were prepared by the O-alkylation reaction of the C(6)-hydroxymethyl templates with appropriate electrophiles as described in above examples.

Example	Compound Name	*m/z* (M+H)
1524	(6R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-ethoxymethyl-piperazin-2-one	513
1525	(6R)-1-(4-Amino-quinazolin-7-ylmethyl)-6-benzyloxymethyl-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-piperazin-2-one	575

Scheme 11 A synthetic scheme of the C(6)-alkylaminomethyl substituted isoxazoylmethyl inhibitors.



Reagents: (a) Ms_2O, Et_3N, CH_2Cl_2. (b) 1. Amine, DMF, 80 °C. 2. c-HCl, MeOH; 3. 1,3,5-Triazine, AcOH, EtOH, reflux. (c) 1. PDC. 2. amines, $NaB(OAc)_3H$, 4A MS, MeOH. 3. see (b.2). (d) see (b.3). (e) 1. Phthalimide, PPh_3, DEAD, THF. 2. Hydrazine. (f) 1. acetone, $NaB(OAc)_3H$, 4A MS. 2. Boc_2O ,THF. (g) 1.see (b.2-3), 2. TFA, CH_2Cl_2.

Example 1526 (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-pyrrolidin-1-ylmethyl-piperazin-2-one

A: (*R*)-Methanesulfonic acid 1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl ester. To a solution of (*R*)-2-(benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-hydroxymethyl-6-oxo-piperazin-1-ylmethyl}-benzonitrile (1.89 g, 3.04 mmol) and Et_3N (2.1 mL, 15.2 mmol) in CH_2Cl_2 (25 mL) was added methane sulfonic anhydride (815 mg, 4.68 mmol). After stirring for 3 h the CH_2Cl_2 was concentrated and the residue was partitioned between EtOAc and water. The EtOAc was washed with water, followed by brine, dried over Na_2SO_4, filtered and concentrated to afford 1.9 g (89%) of (*R*)-methanesulfonic acid 1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl ester as a yellow foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7□□□ (d, *J* = 7.1 Hz, 2H), 7.14-7.52 (m, 10H), 6.94 (d, *J* = 4.0 Hz, 1H), 6.88 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.63 (d, *J* = 1.3 Hz, 1H), 6.35 (s, 1H), 5.12 (d, *J* = 15.1 Hz, 1H), 4.41 (dd, *J* = 10.0, 8.9 Hz, 1H), 4.05-4.16 (m, 1H), 3.91 (d, *J* = 15.1 Hz, 1H), 3.68 (d, *J* = 3.5 Hz, 2H), 3.53 (d, *J* = 16.7 Hz, 1H), 3.21-3.29 (m, 1H), 2.94-3.14 (m, 2H), 2.94 (s, 3H), 2.32-2.38 (m, 1H) ppm. Mass Spectrum: (ESI) *m/z* 700 $(M+H)^+$.

B: (*S*)-2-(Benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-oxo-6-pyrrolidin-1-ylmethyl-piperazin-1-ylmethyl}-benzonitrile. A mixture of (*R*)-methanesulfonic acid 1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl ester (1.5 g, 2.14 mmol), pyrrolidine (2 mL, 24 mmol), and K_2CO_3 (1.55 g, 11.2 mmol) was heated to 80 °C for 2 h. The reaction was diluted with EtOAc which was then washed with water, followed by brine, dried over Na_2SO_4, filtered and concentrated to afford 1.5 g (>100%) of crude (*S*)-2-(benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-oxo-6-pyrrolidin-1-ylmethyl-piperazin-1-ylmethyl}-benzonitrile as an oil. Mass Spectrum: (ESI) *m/z* 675 $(M+H)^+$.

C: (*S*)-2-Amino-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-oxo-6-pyrrolidin-1-ylmethyl-piperazin-1-ylmethyl}-benzonitrile. (*S*)-2-(benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-oxo-6-pyrrolidin-1-ylmethyl-piperazin-1-ylmethyl}-benzonitrile (1.5 g, 2.14 mmol) was dissolved in a mixture of MeOH (20 mL) and CH_2Cl_2 (5 mL) at 0 °C and was treated with TFA (4 mL). The reaction was allowed to warm to ambient temperature and after stirring for 2 h was chromatographed on SiO_2 (CH_2Cl_2 to 10% MeOH / CH_2Cl_2) to give 880 mg (85% over two steps) of (*S*)-2-amino-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-oxo-6-pyrrolidin-1-ylmethyl-piperazin-1-ylmethyl}-benzonitrile as a brown gum. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22-7.29 (m, 2H,), 6.93 (d, *J* = 4.0 Hz, 1H), 6.73 (d, *J* = 1.0 Hz, 1H), 6.56 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.29 (s, 1H), 4.94 (d, *J* = 15.1 Hz, 1H), 4.11 (d, *J* = 15.0 Hz, 1H), 3.72-3.89 (m, 1H), 3.69-3.74 (m, 2H), 3.59 (d, *J* = 17.9 Hz, 1H), 3.27 (d, *J* = 12.7 Hz, 1H), 2.58-2.65 (m, 6H), 2.01-2.07 (m, 4H) ppm.

D: (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-pyrrolidin-1-ylmethyl-piperazin-2-one A solution of (*S*)-2-amino-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-oxo-6-pyrrolidin-1-ylmethyl-piperazin-1-ylmethyl}-benzonitrile (880 mg, 1.72 mmol), HOAc (950 μL, 16.6 mmol), and 1,3,5-triazine (1.40 g, 17.2 mmol) in absolute EtOH (20 mL) was heated to reflux for 16 h. Chromatography on SiO_2 (CH_2Cl_2 to 20% MeOH / CH_2Cl_2) afforded 800 mg (86%) of (*S*)-1-(4-amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-pyrrolidin-1-ylmethyl-piperazin-2-one as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.3 (br s, 1H), 9.81 (d, *J* = 29.3 Hz, 2H), 8.79 (s, 1H), 8.40 (d, *J* = 8.6 Hz, 1H), 7.54-7.65 (m, 3H), 7.27 (d, *J* = 4.0 Hz, 1H), 6.96 (s, 1H), 5.18 (d, *J* = 16.6 Hz, 1H), 4.41 (d, *J* = 16.6 Hz, 1H), 3.39-3.88 (m, 8H), 3.08-3.39 (m, 2H), 2.75 (d, *J* = 11.2 Hz, 1H), 1.80-1.98 (m, 4H) ppm. Mass Spectrum: (ESI) *m/z* 538 $(M+H)^+$.

Example 1527 (*R*)-N-{1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl}-N-(2-isopropoxy-ethyl)-formamidine and (6R)-N-{1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl}-N-(2-isopropoxy-ethyl)-formamide

A: (*R*)-2-(Benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-formyl-6-oxo-piperazin-1-ylmethyl}-benzonitrile. To a solution of (*R*)-2-(benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-hydroxymethyl-6-oxo-piperazin-1-ylmethyl}-benzonitrile (0.8 g, 1.3 mmol) and 4A MS (1 g) in CH_2Cl_2 (20 mL) was added PDC (0.98 g, 2.6 mmol). After 1 h at ambient temperature, the reaction mixture was chromatographed on SiO_2 (CH_2Cl_2 to 1% MeOH / CH_2Cl_2) to afford 520 mg (65%) of (*R*)-2-(benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-formyl-6-oxo-piperazin-1-ylmethyl}-benzonitrile.

B: (*R*)-2-(Benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-[(2-isopropoxy-ethylamino)-methyl]-6-oxo-piperazin-1-ylmethyl}-benzonitrile. To a solution of (*R*)-2-(benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-formyl-6-oxo-piperazin-1-ylmethyl}-benzonitrile (280 mg, 0.45 mmol), 2-aminoethyl isopropyl ether (230 mg, 2.3 mmol), and 4Å molecular sieves (300 mg) in 1,2-dichloroethane (3 mL) was added $NaBH(OAc)_3$ (290 mg, 1.35 mmol). After stirring for 16h the molecular sieves were filtered off, and washed with CH_2Cl_2. The filtrate was then washed with aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated to give (*R*)-2-(benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-[(2-isopropoxy-ethylamino)-methyl]-6-oxo-piperazin-1-ylmethyl}-benzonitrile which was used for next reaction without further purification.

C: (*R*)-2-Amino-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-[(2-isopropoxy-ethylamino)-methyl]-6-oxo-piperazin-1-ylmethyl}-benzonitrile. To a solution of (*R*)-2-(benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-[(2-isopropoxy-ethylamino)-methyl]-6-oxo-piperazin-1-ylmethyl}-benzonitrile in a mixture of MeOH (4 mL) and CH_2Cl_2 (1 mL) at 0 °C was added conc. HCl (5 drops). After stirring for 20 min, the reaction was concentrated, and diluted with saturated $NaHCO_3$ solution and EtOAc. The separated organic phase was washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude residue was chromatographed on silica gel (CH_2Cl_2 to 5% MeOH in CH_2Cl_2) to provide 80 mg (33%) of (*R*)-2-amino-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-[(2-isopropoxy-ethylamino)-methyl]-6-oxo-piperazin-1-ylmethyl}-benzonitrile. Mass Spectrum: (ESI) *m/z* 543 $(M+H)^+$.

D: (*R*)-N-{1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl}-N-(2-isopropoxy-ethyl)-formamidine and (*R*)-N-{1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl}-N-(2-isopropoxy-ethyl)-formamide. To a solution of (*R*)-2-amino-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-[(2-isopropoxy-ethylamino)-methyl]-6-oxo-piperazin-1-ylmethyl}-benzonitrile (80 mg, 0.15 mmol) in absolute ethanol (5 mL) was added 1,3,5-triazine (0.13 g, 2.2 mmol) and acetic acid (0.1 mL, 2.2 mmol). The solution was heated to 90 °C for 20 h and concentrated. The crude material was purified by RP-HPLC eluting with a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 80% CH_3CN/H_2O (0.1% TFA) to give 10 mg (11%) of (*R*)-N-{1-(4-amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl}-N-(2-isopropoxy-ethyl)-formamidine. Mass Spectrum: (ESI) *m/z* 597 $(M+H)^+$, and 25 mg (28%) of (*R*)-N-{1-(4-amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl}-N-(2-isopropoxy-ethyl)-formamide. Mass Spectrum: (ESI) *m/z* 598 $(M+H)^+$.

The following compounds were prepared in a similar fashion according to the above examples.

Example	Compound Name	m/z (M+H)
1528	(*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-pyrrolidin-1-ylmethyl-piperazin-2-one	538
1529	(*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-piperidin-1-ylmethyl-piperazin-2-one	552
1530	(*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-[(cyclopentyl-methyl-amino)-methyl]-piperazin-2-one	566

Example 1531 (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-(isopropylamino-methyl)-piperazin-2-one

A: (*R*)-2-(Benzhydrylidene-amino)-4-[4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile. To a solution of (*R*)-2-(benzhydrylidene-amino)-4-{4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-hydroxymethyl-6-oxo-piperazin-1-ylmethyl}-benzonitrile (2.00 g, 3.22 mmol), triphenylphosphine (2.55 g, 9.72 mmol), and phthalimide (1.86 g, 12.6 mmol) in a mixture of THF (15 mL) and toluene (15 mL) at -70°C was added DEAD (1.45 mL, 9.66 mmol) dropwise.

After warming to ambient temperature and stirring for 16 h, chromatography on SiO_2 (5:1 Hexanes/EtOAc to 1:2 Hexanes/EtOAc) afforded 4.7 g (>100%) of (*R*)-2-(benzhydrylidene-amino)-4-[4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile as a yellow solid. Mass Spectrum: (ESI) *m/z* 751 $(M+H)^+$.

B: (*S*)-4-{2-Aminomethyl-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-1-ylmethyl}-2-(benzhydrylidene-amino)-benzonitrile. To a solution of (*R*)-2-(benzhydrylidene-amino)-4-[4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile (4.7 g, 3.22 mmol) in MeOH (40 mL) at 0 °C was added hydrazine monohydrate (2 mL, 41 mmol). After warming to ambient temperature and stirring for 16 h, the reaction was diluted with water and extracted with EtOAc. The EtOAc was washed with brine, dried over Na_2SO_4, filtered and concentrated. Chromatography on SiO_2 (CH_2Cl_2 to 4% MeOH / CH_2Cl_2) afforded 1.13 g (57% over two steps) of (*S*)-4-{2-aminomethyl-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-1-ylmethyl}-2-(benzhydrylidene-amino)-benzonitrile as an orange solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.72-7.78 (m, 2H), 7.36-7.53 (m, 4H), 7.22-7.29 (m, 4H), 7.12-7.18 (m, 2H), 6.93 (d, *J* = 3.9 Hz, 1H), 6.85 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.60 (d, *J* = 1.2 Hz, 1H), 6.30 (s, 1H), 5.05 (d, *J* = 15.4 Hz, 1H), 4.00 (d, *J* = 15.4 Hz, 1H), 3.46-3.71 (m, 3H), 3.09 (d, *J* = 16.4 Hz, 1H), 2.98 (d, *J* = 11.8 Hz, 1H), 2.66-2.91 (m, 2H), 2.64-2.75 (m, 1H), 2.37-2.42 (m, 1H) ppm. Mass Spectrum: (ESI) *m/z* 621 $(M+H)^+$.

C: (*S*)-2-(Benzhydrylidene-amino)-4-[4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(isopropylamino-methyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile. To a solution of (*S*)-4-{2-aminomethyl-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-1-ylmethyl}-2-(benzhydrylidene-amino)-benzonitrile (1.13 g, 1.82 mmol), glacial acetic acid (104 μL, 1.82 mmol), and acetone (200 μL, 2.7 mmol) was added sodium (triacetoxy)borohydride (553 mg, 2.60 mmol). After stirring for 16 h, the reaction was quenched with sat. $NaHCO_3$ and extracted with EtOAc. The EtOAc was washed with brine, dried over Na_2SO_4, filtered and concentrated to afford 1.09 g (90%) of (*S*)-2-(benzhydrylidene-amino)-4-[4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(isopropylamino-methyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile as a yellow foam. Mass Spectrum: (ESI) *m/z* 663 $(M+H)^+$.

D: (*R*)-{1-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl}-isopropyl-carbamic acid tert-butyl ester. To a

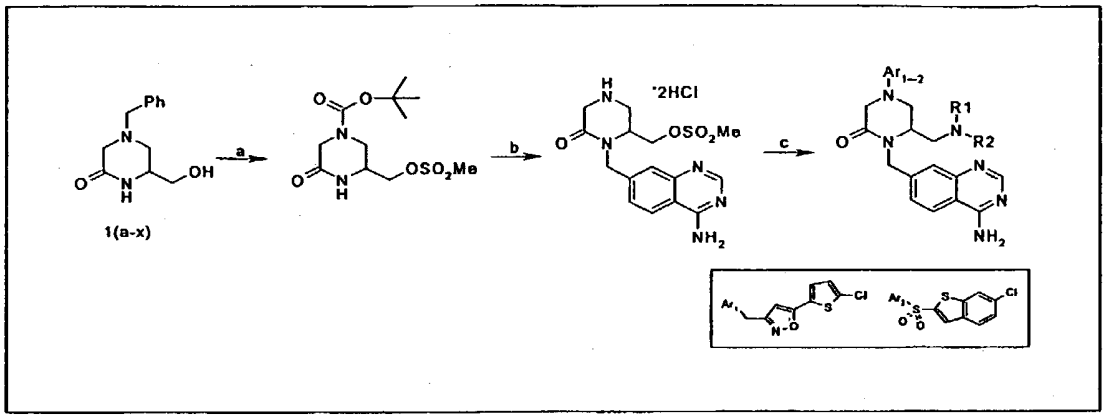
solution of (*S*)-2-(benzhydrylidene-amino)-4-[4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-2-(isopropylamino-methyl)-6-oxo-piperazin-1-ylmethyl]-benzonitrile (1.34 g, 2.02 mmol), Et_3N (560 μL, 4.04 mmol), and DMAP (26 mg, 0.20 mmol) in THF (15 mL) at 0°C was added Boc-anhydride (485 mg, 2.22 mmol). After warming to ambient temperature and stirring for 2 h, Boc-anhydride (144 mg, 0.660 mmol) was added. The reaction was allowed to stir for 48 h and was then diluted with water and extracted with EtOAc. The EtOAc was washed with brine, dried over Na_2SO_4, filtered and concentrated to afford 1.55 g (100%) of (*R*)-{1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl}-isopropyl-carbamic acid tert-butyl ester as a yellow solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.65-7.73 (m, 2H), 7.33-7.50 (m, 4H), 7.19-7.30 (m, 4H), 7.11-7.18 (m, 2H), 6.89-6.95 (m, 2H), 6.81 (s, 1H), 6.28 (s, 1H), 4.98-5.07 (m, 1H), 3.89-4.05 (m, 1H), 3.63 (s, 2H), 3.20-3.60 (m, 5H), 2.76-2.89 (m, 2H), 2.14-2.23 (m, 1H), 1.32-1.54 (m, 9H), 1.03-1.17 (m, 6H) ppm. Mass Spectrum: (ESI) *m/z* 763 $(M+H)^+$.

E: (*R*)-{1-(3-Amino-4-cyano-benzyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl}-isopropyl-carbamic acid tert-butyl ester. To a solution of (*R*)-{1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl}-isopropyl-carbamic acid tert-butyl ester (1.55 g, 2.02 mmol) in a mixture of MeOH (10 mL) and THF (5 mL) at 0°C was added conc. HCl (2 drops). After stirring for 45 min conc. HCl (3 drops) was added and the reaction was allowed to warm to ambient temperature and stir for an additional 1.5 h. Chromatography on SiO_2 (CH_2Cl_2 to 10% MeOH / CH_2Cl_2) afforded 350 mg (29% over two steps) of (*R*)-{1-(3-amino-4-cyano-benzyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl}-isopropyl-carbamic acid tert-butyl ester as a white solid. Mass Spectrum: (ESI) *m/z* 599 $(M+H)^+$.

F: (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-(isopropylamino-methyl)-piperazin-2-one. A solution of (*R*)-{1-(3-amino-4-cyano-benzyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl}-isopropyl-carbamic acid tert-butyl ester (350 mg, 0.584 mmol), glacial acetic acid (340 μL, 5.94 mmol), and 1,3,5-triazine (492 g, 6.07 mmol) in absolute EtOH (10 mL) was heated at reflux for 16 h. The EtOH was concentrated and the residue was dissolved in CH_2Cl_2 (10 mL), cooled to 0°C and treated with TFA (4 mL). After stirring for 16 h at ambient temperature, the mixture was concentrated amd purified by RP-HPLC eluting with a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 70% CH_3CN/H_2O (0.1% TFA). The appropriate product fractions were combined and lyophilized to afford 188 mg (50%) of the TFA salt of (*S*)-1-(4-amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-

thiophen-2-yl)-isoxazol-3-ylmethyl]-6-(isopropylamino-methyl)-piperazin-2-one as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.79 (d, J = 13 Hz, 2H), 8.81 (s, 1H), 8.65 (br s, 1H), 8.50 (br s, 1H), 8.38 (d, J = 8.5 Hz, 1H), 7.53-7.63 (m, 3H), 7.29 (d, J = 4.0 Hz, 1H), 6.94 (s, 1H), 5.17 (d,J = 16.7 Hz, 1H), 4.39 (d, J = 16.7 Hz, 1H), 3.78 (AB quartet, J = 30.0, 14.4 Hz, 2H), 3.46-3.62 (m, 3H), 3.33 (t, J = 5.8 Hz, 1H), 3.09-3.25 (m, 3H), 2.72 (d,J = 10.2 Hz, 1H), 1.14-1.23 (m, 6H) ppm. Mass Spectrum: (ESI) *m/z* 526 $(M+H)^+$.

Scheme 12 A mesylate scheme of the C(6)-alkylaminomethyl substituted inhibitors.



Reagents: (a) 1. Ms_2O, Et_3N, CH_2Cl_2. 2. $Pd(OH)_2$, MeOH, H_2. 3. Boc_2O, Et_3N, THF. (b) 1. NaH, 4-amino-7-bromomethylquinazoline, THF. 2. HCl, MeOH. (c) 1. Et_3N, Ar_1Br or Ar_2SO_2Cl, CH_2Cl_2. 2. Amine, DMF, K_2CO_3, 80 °C.

Example 1532 (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-[(2-methoxy-ethylamino)-methyl]-piperazin-2-one

A: (*R*)-Methanesulfonic acid 4-benzyl-6-oxo-piperazin-2-ylmethyl ester. To a solution of (*R*)-4-benzyl-6-hydroxymethyl-piperazin-2-one (2.0 g, 9.3 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added Et_3N (5.2 mL, 37 mmol), followed by methanesulfonic anhydride (3.24 g, 19 mmol). After 1 h at ambient temperature, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated to provide 2.6 g (94%) (*R*)-methanesulfonic acid 4-benzyl-6-oxo-piperazin-2-ylmethyl ester which was used in the next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3-7.26 (m, 5H), 6.18 (br s, 1H), 4.32-4.16 (m, 2H), 3.8-3.7 (m, 1H), 3.61 (d, J = 12.9 Hz, 1H), 3.52 (d, J = 12.9 Hz, 1H), 3.32 (d, J = 16 Hz, 1H), 3.0 (s, 3H), 2.7-2.6 (m, 2H) ppm. Mass Spectrum: (ESI) *m/z* 299 $(M+H)^+$.

B: (*R*)-Methanesulfonic acid 6-oxo-piperazin-2-ylmethyl ester. To a solution of (*R*)-methanesulfonic acid 4-benzyl-6-oxo-piperazin-2-ylmethyl ester (2.9 g, 9.7 mmol) in MeOH (50

mL) was added 10% palladium hydroxide on C (1 g). The heterogenous mixture was hydrogenated at ambient temperature under a balloon of H_2 for 20 h. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated to afford (*R*)-methanesulfonic acid 6-oxo-piperazin-2-ylmethyl ester which was used directly in the next reaction without further purification. Mass Spectrum: (ESI) *m/z* 209 $(M+H)^+$.

C: (*R*)-3-Methanesulfonyloxymethyl-5-oxo-piperazine-1-carboxylic acid tert-butyl ester. To a suspension of (*R*)-methanesulfonic acid 6-oxo-piperazin-2-ylmethyl ester and $NaHCO_3$ (2.44 g, 29 mmol) in THF/water (5:1, 20 mL) at 0 °C was added Boc-anhydride (2.75 g, 12.6 mmol). After 24 h at ambient temperature, the reaction mixture was diluted with saturated $NaHCO_3$ solution and extracted with EtOAc. The combined organic extracts were washed with saturated NH_4Cl solution and brine, dried ($MgSO_4$), filtered, and concentrated. Chromatography on SiO_2 (1% to 10% MeOH in CH_2Cl_2) provided 1.8 g (35%) of (*R*)-3-methanesulfonyloxymethyl-5-oxo-piperazine-1-carboxylic acid tert-butyl ester. ^1H NMR (300 MHz, $CDCl_3$) δ 7.5 (br s, 1H), 4.3-4.1 (m, 3H), 3.94 (d, J = 19 Hz, 1H), 3.82-3.75 (m, 2H), 3.55 (dd, J = 14.6, 4.6 Hz, 1H), 3.09 (s, 3H), 1.48 (s, 9H) ppm. Mass Spectrum: (ESI)*m/z* 617 $(2M+H)^+$.

D: (*R*)-4-(4-Amino-quinazolin-7-ylmethyl)-3-methanesulfonyloxymethyl-5-oxo-piperazine-1-carboxylic acid tert-butyl ester. To a solution of (*R*)-3-methanesulfonyloxymethyl-5-oxo-piperazine-1-carboxylic acid tert-butyl ester (1.8 g, 5.8 mmol) in DMF (20 mL) at 0 °C was added sodium hydride (a 60% dispersion in mineral oil, 0.35 g, 8.7 mmol) followed after 15 min by 4-amino-7-bromomethyl-quinazoline (1.52 g, 6.4 mmol). After 1 h at ambient temperature, the reaction mixture was quenched with saturated NH_4Cl, and extracted with EtOAc. The combined organic extracts were washed with water (twice), dried ($MgSO_4$), filtered and concentrated. The crude product was chromatographed on SiO_2 (5% to 20% MeOH in CH_2Cl_2) to provide 1.72 g (63%) of (*R*)-4-(4-amino-quinazolin-7-ylmethyl)-3-methanesulfonyloxymethyl-5-oxo-piperazine-1-carboxylic acid tert-butyl ester. Mass Spectrum: (ESI) *m/z* 466 $(M+H)^+$.

E: (*R*)-Methanesulfonic acid 1-(4-amino-quinazolin-7-ylmethyl)-6-oxo-piperazin-2-ylmethyl ester. A solution of (*R*)-4-(4-amino-quinazolin-7-ylmethyl)-3-methanesulfonyloxymethyl-5-oxo-piperazine-1-carboxylic acid tert-butyl ester (1.72 g, 3.7 mmol) in MeOH (80 mL) at 0 °C was bubbled with anhydrous HCl gas for 15 min. After 6 h at ambient temperature, the reaction mixture was concentrated and triturated with MeOH and ether to provide 1.54 g of (*R*)-methanesulfonic acid 1-(4-amino-quinazolin-7-ylmethyl)-6-oxo-piperazin-2-ylmethyl ester as a

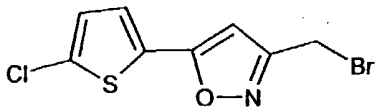
hydrochloride salt which were used in the next reaction without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.32 (d, *J* = 4.0 Hz, 1H), 7.78 (s, 2H), 5.05 (br s, 1H), 4.56 (br s, 1H), 4.46 (br s, 1H), 4.27 (br s, 1H), 4.07 (br s, 2H), 3.76 (br s, 2H), 3.11 (s, 3H) ppm. Mass Spectrum: (ESI) *m/z* 366 $(M+H)^+$.

F: (*R*)-Methanesulfonic acid 1-(4-amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b] thiophene-2-sulfonyl)-6-oxo-piperazin-2-ylmethyl ester. To a solution of (*R*)-methanesulfonic acid 1-(4-amino-quinazolin-7-ylmethyl)-6-oxo-piperazin-2-ylmethyl ester-HCl (0.48 g, 1.1 mmol) in DMF (3 mL) at 0 °C was added Et_3N (0.92 mL, 6.6 mmol), followed by 6-chloro-benzo[b]thiophene-2-sulfonyl chloride (330 mg, 1.32 mmol). After 0.5 h at ambient temperature, the reaction mixture was diluted with water to give a solid which was filtered and washed with ether. The crude (*R*)-methanesulfonic acid 1-(4-amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-ylmethyl ester (0.7 g, 100%) was used in the following reaction without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.37 (s, 1H), 8.33 (s, 1H), 8.22 (s, 1H), 8.11 (s, 1H), 8.07 (s, 1H), 7.72 (br s, 1H), 7.59 (d,*J* = 9.9 Hz, 1H), 7.51 (s, 1H), 7.32 (d, *J* = 9.9 Hz, 1H), 5.15 (d, *J* = 16 Hz, 1H), 4.45-4.30 (m, 3H), 4.07 (d, *J* = 18 Hz, 1H), 3.85-3.70 (m, 3H), 3.25 (s, 3H), 3.25-3.15 (m, 1H). Mass Spectrum: (ESI)*m/z* 596 $(M+H)^+$.

G: (*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-[(2-methoxy-ethylamino)-methyl]-piperazin-2-one A mixture of (*R*)-methanesulfonic acid 1-(4-amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-ylmethyl ester (100 mg, 0.17 mmol) and 2-aminoethyl methyl ether (1 ml) in DMF (2 ml) was heated to 100 °C for 24 h. The reaction mixture was concentrated and chromatographed on SiO_2 (5% to 20% MeOH in CH_2Cl_2) to provide 20 mg (20%) of (*S*)-1-(4-amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-[(2-methoxy-ethylamino)-methyl]-piperazin-2-one. ^{1}H NMR (300 MHz, DMSO-d_6) ↗ 9.77 (br. s, 2H), 8.96 (br. s, 2H), 8.81 (s, 1H), 8.39 (s, 1H), 8.31 (d, *J* = 8.6 Hz, 1H), 8.22 (s, 1H), 8.11 (d, *J* = 8.7 Hz, 1H), 7.65-7.58 (m, 3H), 5.14 (d, *J* = 16.8 Hz, 1H), 4.44 (d, *J* = 16.8 Hz, 1H), 4.10-3.80 (m, 5H), 3.68 (d, *J* = 16.2 Hz, 1H), 3.61 (t, *J* = 4.8 Hz, 2H), 3.50-3.20 (m, 4H), 3.32 (s, 3H) ppm. Mass Spectrum: (ESI)*m/z* 575 $(M+H)^+$.

Preparations of Methylhalides

Preparation of 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole



Part A. 4-(5-Chloro-thiophen-2-yl)-2,4-dioxo-butyric acid ethyl ester.

Sodium hydride (60% dispersion in mineral oil, 2.43 g, 60.8 mmol) was added to the solution of 2-acetyl-5-chlorothiophene (4.88 g, 30.4 mmol) in 150 ml of anhydrous toluene at 0 °C under nitrogen in two portions. After the mixture was stirred at 0 °C for 10 minutes, diethyl oxalate (6.20 ml, 45.6 mmol) was added via syringe, the resulting mixture was stirred at 0 °C for half an hour, then heated to 140 °C gradually and refluxed for 1 hour. The solvents were removed under reduced pressure, 250 ml of water was added to the residue which was then washed with ethyl acetate (75 ml x 2), the aqueous portion was cooled to 0 °C and to which was added 2N HCl till PH = 2, ethyl acetate was used to extract the acidified aqueous portion (100 ml x 4), the combined organic portions were then washed with brine, dried with $MgSO_4$. Removal of the solvents afforded the desired product as a brownish solid, 7.10 g, which was used in the following reaction without further purification, 90%. ^1H NMR (CD_3OD) δ 1.36 (t, 3H, J = 7.1 Hz), 4.35 (q, 2H, J = 7.1 Hz), 6.95 (s, 1H), 7.15 (m, 1H), 7.87 (m, 1H).

Part B. 5-(5-chloro-thiophen-2-yl)-isoxazole-3-carboxylic acid ethyl ester.

The mixture of -(5-Chloro-thiophen-2-yl)-2,4-dioxo-butyric acid ethyl ester (5.40 g, 20.7 mmol) and hydroxylamine hydrochloride (5.04 g, 72.5 mmol) in 150 ml of anhydrous ethanol was refluxed for three hours. The solvents were removed under reduced pressure, 150 ml of H2O was added to the residue, followed by ammonium hydroxide (28-30 %) till PH=7. The aqueous mixture was then extracted with ethyl acetate (75ml x3), the combined organic portions were washed with brine, dried with $MgSO_4$. After the solvents were removed, the crude product was purified flash column chromatography (10% of ethyl acetate/hexanes), 4.35 g of the desired product was obtained as a pale solid, 82%. ^1H NMR ($CDCl_3$) δ 1.41 (t, 3H, J = 7.1 Hz), 4.44 (q, 2H, J = 7.1 Hz), 6.71 (s, 1H), 6.95 (d, 1H, J = 4.0 Hz), 7.31 (d, 1H, J = 4.0 Hz).

Part C. [5-(5-chloro-thiophen-2-yl)-isoxazol-3-yl]-methanol.

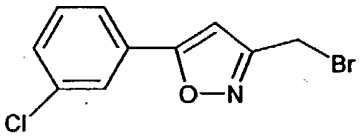
Sodium borohydride (3.20 g, 84.4 mmol) was added to the solution of 5-(5-chloro-thiophen-2-yl)-isoxazole-3-carboxylic acid ethyl ester (4.35 g, 16.9 mmol) in 80 ml of anhydrous ethanol at 0 °C, the mixture was then stirred at room temperature for 12 hours. Ethanol was removed under reduced pressure, the residue was taken up in H_2O (100ml), and NH_4Cl (aq)

was added to consume the excess $NaBH_4$. The product was extracted with ethyl acetate (75ml x 3), the combined organic portions were washed with brine, dried with $MgSO_4$, removal of the solvents afforded 3.53 g of white solid as the desired product, 97%. ^1H NMR ($CDCl_3$) δ 4.78 (s, 2H), 6.40 (s, 1H), 6.94 (d, 1H, J = 3.9 Hz), 7.27 (d, 1H, J = 3.9 Hz).

Part D. 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole.

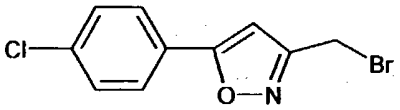
NBS (3.19 g, 17.9 mmol) was added to the mixture of 5-(5-chloro-thiophen-2-yl)-isoxazol-3-yl]-methanol (3.50 g, 16.2 mmol) and triphenyl phosphine (4.68 g, 17.9 mmol) in 80 ml of anhydrous methylene chloride at 0 °C. The mixture was then stirred at room temperature for 1 hour. The solvents were removed, the residue was purified by flash column chromatography (10 % of ethyl acetate/hexanes), 4.0 g of the product was obtained as a white solid, 89%. ^1H NMR ($CDCl_3$) δ 4.42 (s, 2H), 6.42 (s, 1H), 6.95 (d, 1H, J = 4.0 Hz), 7.28 (d, 1H, J = 4.0 Hz).

Preparation of 3-Bromomethyl-5-(3-chloro-phenyl)-isoxazole



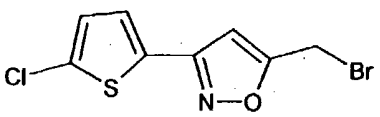
3-Bromomethyl-5-(3-chloro-phenyl)-isoxazole was prepared according to the methods described for 3-methyl-5-(5-chloro-thiophen-2-yl)-1H-pyrazole. ^1H NMR ($CDCl_3$) δ 4.46 (s, 2H), 6.64 (s, 1H), 7.41-7.43 (m, 2H), 7.64-7.67 (m, 1H), 7.77 (m, 1H).

Preparation of 3-Bromomethyl-5-(4-chlorophenyl)-isoxazole



3-Bromomethyl-5-(4-chlorophenyl)-isoxazole was prepared according to the methods described for 3-methyl-5-(5-chloro-thiophen-2-yl)-1H-pyrazole. ^1H NMR ($CDCl_3$) δ 4.45 (s, 2H), 6.60 (s, 1H), 7.44 (d, 2H, J=8.6 Hz), 7.70(d, 2H, J= 8.6 Hz).

Preparation of 5-bromomethyl-3-(5-chloro-thiophen-2-yl)-isoxazole



Method I:

Part A. 5-Chloro-thiophene-2-carbaldehyde oxime.

A mixture of 5-chloro-2-thiophene carboxaldehyde (1.36 g, 9.28 mmol) and hydroxyamine hydrochloride (0.71 g, 10.2 mmol) in 8 ml of pyridine was stirred at room temperature overnight. Pyridine was removed under reduced pressure, the residue was purified by flash column chromatography (5% -10% of ethyl acetate in methylene chloride), 1.02 g of the product was obtained as a white solid, 68%. ^{1}H NMR (CD_3OD) δ 6.94 (d, 1H, J=4.0 Hz), 7.14 (d, 1H, J=4.0 Hz), 7.60 (s, 1H), 8.81 (broad, 1H, OH).

Part B. 5-Bromomethyl-3-(5-chloro-thiophen-2-yl)-isoxazole

N-chlorosuccinimide (0.28 g, 2.10 mmol) was added to the solution of 5-Chloro-thiophene-2-carbaldehyde oxime (0.33 g, 2.04 mmol) in 10 ml of anhydrous DMF at room temperature under N_2, followed by the addition of two drops of pyridine. The mixture was stirred at r.t. for one hour, at 60 °C for 3 hours, the mixture was cooled to 0 °C and to which was added propargyl bromide (80 wt. % in toluene, 2.30 ml, 20.4 mmol), a solution of triethyl amine (0.29 ml, 2.04 mmol) in 2.5 ml of DMF was then added dropwise slowly in a period of 25 minutes . The reaction was warmed to room temperature and stirred for 18 hours, diluted with water (200 ml), extracted with ethyl acetate (50ml x 3), the combined organic portions were washed with water (100 ml x 2), brine, dried with $MgSO_4$. After the solvents were removed, the crude product was purified flash column chromatography (5%-10% of ethyl acetate/hexanes), 0.28 g of the desired product was obtained as a white solid, 49%. ^{1}H NMR ($CDCl_3$) δ 4.46 (s, 2H), 6.51 (s, 1H), 6.92 (d, 1H, J = 3.9 Hz), 7.19 (d, 1H, J = 3.9 Hz).

Method II:

Part A. 3-(5-chloro-thiophen-2-yl)-isoxazole-5-carboxylic acid ethyl ester.

N-chlorosuccinimide (0.32 g, 2.41 mmol) was added to the solution of 5-Chloro-thiophene-2-carbaldehyde oxime (0.39 g, 2.41 mmol) in 10 ml of anhydrous DMF at room temperature under N_2, followed by the addition of two drops of pyridine. After stirred at 60 °C for 3 hours, the mixture was cooled to 0 °C and to which was added methyl propiolate (1.0 ml, 12.1 mmol), a solution of triethyl amine (0.34 ml, 2.41 mmol) in 2.5 ml of DMF was then added slowly in a period of 30 minutes . The reaction was warmed to room temperature and stirred for 12 hours, diluted with water (200 ml), extracted with ethyl acetate (50ml x 2), the combined organic portions were washed with water, brine, dried with $MgSO_4$. After the solvents were removed, the crude product was purified flash column chromatography (3%-10% of ethyl acetate/hexanes), 0.19 g of the desired product was obtained as a white solid, 32%. ^{1}H NMR ($CDCl_3$) δ 3.99 (s, 3H), 6.95 (d, 1H, J=3.9 Hz), 7.11 (s, 1H), 7.26 (d, 1H, J=3.9 Hz).

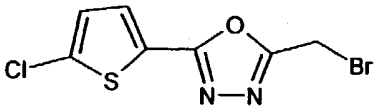
Part B. [3-(5-chloro-thiophen-2-yl)-isoxazol-5-yl]-methanol.

Sodium borohydride (0.14 g, 3.90 mmol) was added to a suspension of 3-(5-chloro-thiophen-2-yl)-isoxazole-5-carboxylic acid ethyl ester (0.19 g, 0.78 mmol) in 15 ml of anhydrous methanol at 0 °C. The mixture was then stirred at 0 °C under N_2, at room temperature for half an hour. Methanol was removed under reduced pressure, the residue was taken up in H_2O (50ml), and NH_4Cl (aq) was added until pH = 7 was obtained. The product was extracted with ethyl acetate (30 ml x 2), the combined organic portions were washed with brine, dried with $MgSO_4$, removal of the solvents afforded 0.14 g of white solid as the desired product, 83%. ^1H NMR ($CDCl_3$) δ 4.79 (s, 2H), 6.44 (s, 1H), 6.92 (d, 1H, J = 3.9 Hz), 7.19 (d, 1H, J = 3.9 Hz).

Part C. 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole.

N-bromosuccinimide (0.14 g, 0.78 mmol) was added to the mixture of [3-(5-chloro-thiophen-2-yl)-isoxazol-5-yl]-methanol (0.14 g, 0.65 mmol) and triphenyl phosphine (0.21 g, 0.78 mmol) in 15 ml of anhydrous methylene chloride at 0 °C under N_2. The mixture was then stirred at room temperature for 1 hour. The solvents was removed, the residue was purified by flash column chromatography (10 % of ethyl acetate/hexanes), 0.13 g of the product was obtained as a white solid, 72%. ^1H NMR ($CDCl_3$) δ 4.46 (s, 2H), 6.51 (s, 1H), 6.92 (d, 1H, J = 3.9 Hz), 7.19 (d, 1H, J = 3.9 Hz).

Preparation of 5-(5-chlorothiophen-2-yl)-2-bromomethyl-[1,3,4]oxadiazole



Part A. 5-chloro-thiophene-2-carboxylic acid N-acetyl-hydrazide.

A 2.0 M solution of oxalyl chloride in methylene chloride (82ml) was added to a stirred solution of 5-chloro-thiophene-2-carboxylic acid (13.33 g) and DMF (0.1 ml) in methylene chloride (150 ml) at
0°C for 25 min., then warmed up to room temperature and stirred for an hour. Evaporated off methylene chloride to give an oil (the acid chloride) which was dissolved in THF (40 ml). He resulting solution was added to a stirred solution of acetyl hydrazide (6.08 g) in THF (100 ml) under N_2 at room temperature, followed by addition of K_2CO_3 (22.66 g). Stirred at room temperature for 4 hours. The THF was removed under vacuum to give a solid that was dissolved in methanol (120 ml). The precipitated solid was removed by filtration; the resulting

solution was concentrated to give the title product (17.90 g) in 100 % yield. ^{1}HNMR (CD_3OD) ppm 7.34 (d, H), 6.85 (d, H), 2.00 (s, 3H).

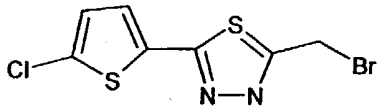
Part B. 5-(5-chloro-thiophen-2-yl)-2-methyl-[1,3,4]oxadiazole

A mixture 5-chloro-thiophene-2-carboxylic acid N-acetyl-hydrazide (1.11 g) and P_2O_5 (18.0 g) was heated to 110°C for 20 hours. Cooling to room temperature and ice (200 g) was added to dissolve P_2O_5. The dark solution was diluted to 400 ml with water and extracted with ether (2x30 ml). The combined organic solution was washed with Brine and dried over $MgSO_4$. After concentration, 0.62 g of product was obtained in 61% yield. ^{1}HNMR ($CDCl_3$) ppm 7.45 (d,H), 6.93 (d, H), 2.56 (s, 3H).

Part C. 5-(5-chloro-thiophen-2-yl)-2-bromomethyl-[1,3,4]oxadiazole

A solution of 5-(5-chloro-thiophen-2-yl)-2-methyl-[1,3,4]-oxadiazole (937 mg), NBS (800 mg) and benzene peroxide (330 mg) in CCl4 (100 ml) was refluxed overnight. The reaction mixture was concentrated to give a solid residue that was chromatographed through silica-gel using 5-10% ethyl acetate as an eluent. The pure product (429 mg) was obtained in 50% yield. ^{1}HNMR ($CDCl_3$) ppm 7.55 (d. H), 6.98 (d, H), 4.58 (s, 2H).

Preparation of 5-(5-chlorothiophen-2-yl)-2-bromomethyl-[1,3,4]thiadiazole



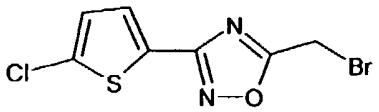
Part A. 5-(5-chloro-thiophen-2-yl)-2-methyl-[1,3,4]thiadiazole

A solution of 5-chloro-thiophene-2-carboxylic acid N-acetyl-hydrazide (1.18 g) and Lowesson's Reagent (2.18 g) in xylene (40 ml) was stirred at 140°C for an hour. The hot solution was transfer into a chromatographic column with silica gel. After cooling, washed with hexane to remove xylene. The solid was chromatographed through silica gel using 20% ethyl acetate as an eluent. Pure product (1.18 g) was obtained in about 100% yield. ^{1}HNMR ($CDCl_3$) ppm 7.25 (d, H), 6.93 (d, H), 2.78 (s, 3H).

Part B. Preparation of 5-(5-chloro-thiophen-2-yl)-2-bromomethyl-[1,3,4] thiadiazole

A solution of 5-(5-chloro-thiophen-2-yl)-2-methyl-[1,3,4]thiadiazole (937 mg), NBS (800 mg) and benzene peroxide (330 mg) in CCl4 (100 ml) was refluxed overnight. Concentrated to give a solid that was chromatographed through silica gel using 10% ethyl acetate as an eluent. The pure product (672 mg) was obtained in 54 % yield. ^{1}HNMR ($CDCl_3$) ppm 7.31 (d. H), 6.96 (d, H), 4.80 (s, 2H).

Preparation of 5-bromomethyl-3-(5-chloro-thiophen-2-yl)-[1,2,4]oxadiazole



Part A. 5-Chloro-thiophene-2-carbaldehyde oxime.

A mixture of 5-chloro-2-thiophene carboxaldehyde (1.36 g, 9.28 mmol) and hydroxyamine hydrochloride (0.71 g, 10.2 mmol) in 8 ml of pyridine was stirred at room temperature overnight. Pyridine was removed under reduced pressure, the residue was purified by flash column chromatography (5% -10% of ethyl acetate in methylene chloride), 1.02 g of the product was obtained as a white solid, 68%. ^{1}H NMR (CD_3OD) δ 6.94 (d, 1H, J=4.0 Hz), 7.14 (d, 1H, J=4.0 Hz), 7.60 (s, 1H), 8.81 (broad, 1H, OH).

Part B. 5-Chloro-thiophene-2-carbonitrile.

5-Chloro-thiophene-2-carbaldehyde oxime (2.20g, 13.6 mmol), in 30 ml of anhydrous acetic anhydide, was refluxed for 24 hours; the excess acetic anhydride was removed under reduced pressure. The resulting residue was taken up in 100 ml of H_2O, neutralized with ammonium hydroxide and extracted with ethyl acetate (50 ml x 3). The combined organic portions were washed with brine.. After the solvents were removed, the residue was purified by flash column chromatography (10% of ethyl acetate in hexanes); 1.50 g of the desired product was obtained as a colorless oil, 77%. ^{1}H NMR ($CDCl_3$) d, J = 4.1 Hz), 6.95 (1H, d, J = 4.0 Hz).

Part C. 5-Chloro-N-hydroxy-thiophene-2-carboxamidine.

A mixture of hydroxyamine hydrochloride (1.10 g, 15.7 mmol) and sodium hydroxide (0.63 g, 15.7 mmol) in 20 ml of ethanol and 1 ml of water was added to the solution of 5-Chloro-thiophene-2-carbonitrile (1.50 g, 10.4 mmol) in 20 ml of ethanol. The mixture was then refluxed for 12 hours. The solvents were removed under reduced pressure and the residue was purified by flash column chromatography (2% of methanol in methylene chloride); 1.65 g of the desired product was obtained as a white solid, 90%. ^{1}H NMR (CD_3OD) δ 7.52 (1H, d, J = 4.1 Hz), 7.00 - 7.01 (1H, m).

Part D. 3-(5-chloro-thiophen-2-yl)-[1,2,4]oxadiazole-5-carboxylic acid ethyl ester.

Pyridine (0.14 ml, 1.70 mmol) was added dropwise to a mixture of 5-Chloro-N-hydroxy-thiophene-2-carboxamidine (0.15 g, 0.85 mmol) and ethyl chlorooxoacetate (0.19 ml, 1.70 mmol) in 10 ml of anhydrous chloroform. The reaction was refluxed for 16 hours; the solvents

were removed under reduced pressure. The residue was taken up in 50 ml of water and extracted with ethyl acetate (15 ml x 2); the organic portion was washed with brine and dried with MgSO4. After concentration the crude product was purified by flash column chromatography (5% of ethyl acetate in hexanes); 0.11 g of the desired product was obtained as a colorless oil, 50%. ^{1}H NMR ($CDCl_3$) δ 7.67 - 7.69 (1H, m), 6.99 (1H, d, J = 4.1 Hz), 4.56 (2H, q, J = 7.1 Hz), 1.48 (3H, t, J = 7.1 Hz).

Part E. [3-(5-chloro-thiophen-2-yl)-4,5-dihydro-[1,2,4]oxadiazol-5-yl]-methanol.

Sodium borohydride (0.080 g, 2.20 mmol) was added to the solution of 3-(5-chloro-thiophen-2-yl)-[1,2,4]oxadiazole-5-carboxylic acid ethyl ester (0.11 g, 0.43 mmol) in 10 ml of anhydrous methanol at 0 °C. The reaction was stirred at 0 °C for 30 minutes, the solvent was removed under reduced pressure and the residue was diluted with 30 ml of water. The aqueous solution was extracted with ethyl acetate (20 ml x 2), the combined organic portions were washed with brine, dried with $MgSO_4$ and concentrated to afford the desired product as a viscous oil (0.085g, 91%). 1H NMR (CD_3OD) δ 7.25 - 7.28 (1H, m), 6.99 - 7.01 (1H, m), 5.61 - 5.62 (1H, m), 3.54 - 3.59 (2H, m).

Part F. 3-(5-Chloro-thiophen-2-yl)-[1,2,4]oxadiazol-5-yl]-methanol.

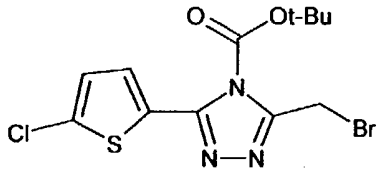
N-Chlorosuccinimide (0.052 g, 0.39 mmol) was added to the soulition of [3-(5-chloro-thiophen-2-yl)-4,5-dihydro-[1,2,4]oxadiazol-5-yl]-methanol (0.085 g, 0.39 mmol) in 4.0 ml of anhydrous DMF at 50 °C under N_2. The mixture was then stirred at 50 °C for 40 minutes, poured into 50 ml of water and extracted with ethyl acetate (15 ml x 3). The combined organic portions were washed with water, brine and dried with $MgSO_4$; removal of the solvents afforded product as a white solid (0.082 g, 96 %). 1H NMR (CD_3OD) δ 7.61 (1H, d, J = 4.0 Hz), 7.09 (1H, d, J = 3.9 Hz), 4.86 (2H, s).

Part G. 5-Bromomethyl-3-(5-chloro-thiophen-2-yl)-1,2,4-oxadiazole.

N-Bromosuccinimide (0.082 g, 0.46 mmol) was added to a mixture of the 3-(5-Chloro-thiophen-2-yl)-[1,2,4]oxadiazol-5-yl]-methanol (0.082 g, 0.38 mmol) and triphenyl phosphine (0.12 g, 0.46 mmol) in 10 ml of anhydrous methylene chloride at 0 °C under N_2. The reaction was stirred at 0 °C for 30 minutes and warmed to ambient temperature for 1 hour. The solvent was removed, the residue was purified by flash column chromatography (5% - 10% of ethyl acetate in hexanes); 0.030 g (47%) of the product was obtained as a colorless oil. Starting

material (0.036 g) was also recovered. ^{1}H NMR ($CDCl_3$) δ 7.58 (1H, d, J = 4.0 Hz), 6.97 (1H, d, J = 4.0 Hz), 4.51 (2H, s).

Preparation of 5-(5-chloro-thiophen-2-yl)-3-bromomethyl-4-carboxylic acid tert-butyl ester[1,2,4]triazole



Part A. N, N'-(5-chloro-thiophen-2-carboxyll-acetyl-hydrazide

A solution of acetic hydrazide (1.62 g) and 1.9 M Et_3Al (25.3 ml) in toluene was stirred at room temperature for 20 min. A solution of 5-chloro-2-cyanothiophene (3.14 g) in toluene (55 ml) was added slowly at room temperature, then stirred at 85°C overnight. The reaction was cooled to room temperature, quenched with 4 drops of water, then stirred at room temperature for 20 min. Water (30 ml) was added, the solid was filtered off and washed with hot methanol (3x30 ml). The filtrate was concentrated; the solid was recrystallized from ethanol to give product as a white solid (2.88g, 61 %). ^{1}HNMR (CD_3OD) ppm 7.35 (d,H), 6.92 (d, H), 2.01 (s, 3H).

Part B. 5-(5-chloro-thiophen-2-yl)-2-methyl-4H-[1,2,4]triazole

N, N'-(5-chloro-thiophen-2-carboxyll-acetyl-hydrazide (1.80 g) was heated at 180°C for 20 min., then cooled to give product as a white solid (1.15 g, 100%). ^{1}HNMR ($CDCl_3$) ppm 7.48 (d, H), 6.96 (d, H), 4.86 (s, NH)2.46 (s, 3H).

Part C. 5-(5-chloro-thiophen-2-yl)-2-methyl-4-carboxylic acid tert-butyl ester[1,2,4]triazole

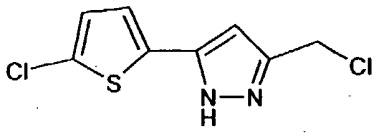
A solution of 5-(5-chloro-thiophen-2-yl)-2-methyl-4H-[1,2,4]triazole (1.09 g), $(BOC)_2O$ (1.43 g) and DMAP (0.14 g) was stirred at room temperature overnight. Evaporation of the THF gives an oil which is dissolved in methylene chloride (40 ml) and washed with 1 N HCl solution and water. After drying ($MgSO_4$) the organic layer isconcentrated to give pure product (1.64 g, 100%). ^{1}HNMR ($CDCl_3$) ppm 7.50 (d, H), 6.89 (d, H), 2.69 (s, 3H), 1.64 (s, 9H).

Part D. 5-(5-chloro-thiophen-2-yl)-3-bromomethyl-4-carboxylic acid tert-butyl ester[1,2,4]triazole

A solution of 5-(5-chloro-thiophen-2-yl)-2-methyl-4-carboxylic acid tert-butyl ester[1,2,4]triazole (1.16 g), NBS (1.14 g) and benzene peroxide (0.27 mg) in CCl_4 (50 ml) was refluxed overnight. Concentration gives a solid, which was chromatographed through silica gel

using 5-10% ethyl acetate as an eluent. The pure product (0.91 g) was obtained in 43% yield. ^{1}HNMR ($CDCl_3$) ppm 7.56 (d. H), 6.92 (d, H), 4.76 (s, 2H), 1.70 (s, 9H).

Preparation of 5-chloromethyl-3-(5-chloro-thiophen-2-yl)-1H-pyrazole



Part A. 4-(5-Chloro-thiophen-2-yl)-2,4-dioxo-butyric acid ethyl ester.

Sodium hydride (60% dispersion in mineral oil, 2.43 g, 60.8 mmol) was added to the solution of 2-acetyl-5-chlorothiophene (4.88 g, 30.4 mmol) in 150 ml of anhydrous toluene at 0 °C under nitrogen in two portions. After the mixture was stirred at 0 °C for 10 minutes, diethyl oxalate (6.20 ml, 45.6 mmol) was added via syringe, the resulting mixture was stirred at 0 °C for half an hour, then heated to 140 °C gradually and refluxed for 1 hour. The solvents were removed under reduced pressure, 250 ml of water was added to the residue which was then washed with ethyl acetate (75 ml x 2), the aqueous portion was cooled to 0 °C and to which was added 2N HCl till PH = 2, ethyl acetate was used to extract the acidified aqueous portion (100 ml x 4), the combined organic portions were then washed with brine, dried with $MgSO_4$. Removal of the solvents afforded the desired product as a brown solid , 7.10g, which was used in the following reaction without further purification, 90%. ^{1}H NMR (CD_3OD) δ 1.36 (t, 3H, J = 7.1 Hz), 4.35 (q, 2H, J = 7.1 Hz), 6.95 (s, 1H), 7.15 (m, 1H), 7.87 (m, 1H).

Part B. 4-(5-chloro-thiophen-2-yl)-2H-pyrazole-3-carboxylic acid ethyl ester.

Hydrazine (0.30 ml, 9.44 mmol) was added to a solution of 4-(5-Chloro-thiophen-2-yl)-2,4-dioxo-butyric acid ethyl ester (1.64 g, 6.30 mmol) in 80 ml of anhydrous ethanol at 0 °C. The mixture was warmed to room temperature, several drops of acetic acid was added and the mixture was stirred at 90 °C for 1 hour. The solvents were removed under reduced pressure, the residue was taken up in 100 ml of H_2O, and extracted with ethyl acetate (50 ml x3). The combined organic portions were washed with brine and dried with $MgSO_4$. After the solvents were removed, the crude product was purified flash column chromatography (10% to 20% of ethyl acetate/hexanes); 0.53 g of the desired product was obtained as a white solid, 33%. ^{1}H NMR ($CDCl_3$) δ 1.38 (t, 3H, J = 7.1 Hz), 4.39 (q, 2H, J = 7.1 Hz), 6.87 (d, 1H, J=3.9 Hz), 6.94 (s, 1H), 7.11 (d, 1H, J = 3.9 Hz), 11.6 (broad, 1H)

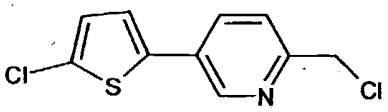
Part C. [5-(5-chloro-thiophen-2-yl)-2H-pyrazol-3-yl]-methanol.

Diisobutylaluminum hydride (1.5 M solution in toluene, 6.80 ml, 10.1mmol) was added dropwise to a solution of 4-(5-chloro-thiophen-2-yl)-2H-pyrazole-3-carboxylic acid ethyl ester (0.52 g, 2.03 mmol) in 40 ml of anhydrous tetrahydrofuran at 0 °C, under nitrogen. The mixture was stirred at 0 °C for half an hour, then at room temperature for half an hour. The reaction was quenched with methanol (0.80 ml) at -10 °C; 100 ml of 10% potassium sodium tartrate solution was added. The aqueous mixture was extracted with ethyl acetate (50 mlx3); the combined organic portions were washed with brine and dried with $MgSO_4$ and concentrated to afford 0.43 g of white solid as the desired product (99%). ^1H NMR (CD_3OD) δ 4.61 (s, 2H), 6.46 (s, 1H), 6.92 (d, 1H, J = 3.7 Hz), 7.13 (d, 1H, J = 3.9 Hz).

Part D. 5-chloromethyl-3-(5-chloro-thiophen-2-yl)-1H-pyrazole.

N-Chlorosuccinimide (0.30 g, 2.24 mmol) was added to the mixture of [5-(5-chloro-thiophen-2-yl)-2H-pyrazol-3-yl]-methanol (0.40 g, 1.86 mmol) and triphenyl phosphine (0.59 g, 2.24 mmol) in 40 ml of anhydrous tetrahydrofuran and 40 ml of anhydrous chloroform at 0 °C under nitrogen. The mixture was then stirred at 0 °C for 10 minutes and warmed to room temperature for half an hour. The solvents were removed, the residue was purified by flash column chromatography (15 % of ethyl acetate/hexanes) and 0.29 g of product was obtained as a white solid (67%). ^1H NMR ($CDCl_3$ with a small amount of CD_3OD) δ 4.58 (s, 2H), 6.42 (s, 1H), 6.84 (d, 1H, J = 3.9 Hz), 7.03 (d, 1H, J = 3.8 Hz).

Preparation of 2-Chloromethyl -5-(5-chloro-thiophen-2-yl)-pyridine hydrochloride



.HCl

Part A. 2-Methyl-5-Trifluoromethylsulfonyloxy-pyridine

2-Methyl-5-hydroxypyridine (7.4 g, 67.80 mmol) was suspended in 40 mL of pyridine. Trifluoromethanesulfonic anhydride (20 g, 70.89 mmol) was added dropwise at 5 °C. After 30 min at this temperature the resulting solution was stirred 12 hours at room temperature.The reaction mixture was diluted with 200 mL of AcOEt, washed with 1N hydrochloric acid (3 x 200 mL), brine (200 mL), dried over magnesium sulfate and concentrated. The titled compound (12.6 g, 77%) was obtained as a colorless liquid. $C_7H_6F_3O_3S$ MS $(M+H)^+ = 242$

Part B. 5-(5-Chloro-thiophen-2-yl)-2-methyl-pyridine

To a solution of 2-Methyl-5-Trifluoromethylsulfonyloxy-pyridine (4.82 g, 20 mmol) in 60 mL of DMF was added 5-chlorothiophene-2-boronic acid (4 g, 24.6 mmol), tetrakis(triphenyl-

phosphine) palladium(0) (1 g, 0.86 mmol) and potassium phosphate (6.36 g, 30 mmol) under nitrogen. The mixture is heated at 100 °C for 6 hours, cooled and diluted with 200 mL of EtOAc. The EtOAc solution was washed with water (2 x 200 mL), brine (200 mL), dried over magnesium sulfate and concentrated. The resulting residue was purified by column chromatography on silica gel eluting with Cyclohexane70 %/ AcOEt 30%. The title compound (3 g, 71%) was obtained as a pale yellow solid. $C_{10}H_8NClS$ MS $(M+H)^+$ = 210, Cl pattern

Part C. 5-(5-Chloro-thiophen-2-yl)-2-methyl-pyridine-1-oxide

To a solution of 5-(5-Chloro-thiophen-2-yl)-2-methyl-pyridine (1.3 g, 6.35 mmol) in 50 mL of CH_2Cl_2 at 5 °C was added portionwise 70% chloroperoxybenzoic acid (1.67g, 6.77 mmol). The resulting solution was stirred at room temperature for 2 hours and concentrated under vacuum. The resulting solid was taken-up in EtOAc (100 mL), washed with 0.5 N NaOH (2x50 mL) and brine (50 mL). The organic layer was dried over magnesium sulfate and concentratedto give the title compound (1.25 g, 71%) as a white solid. $C_{10}H_8OClNS$ MS $(M+H)^+$ = 226, Cl pattern

Part D. 5-(5-Chloro-thiophen-2-yl)-2-hydroxymethyl-pyridine

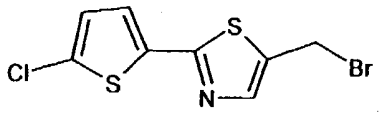
To a solution of 5-(5-Chloro-thiophen-2-yl)-2-methyl-pyridine-1-oxide (1.25 g, 5.54 mmol) in 20 mL of CH_2Cl_2 was added, dropwise, trifluoroacetic anhydride (1.6 mL, 14.07 mmol). The solution was stirred 2 hours at room temperature, concentrated and dried under vacuum. The resulting solid was taken-up in 20 mL of CH_2Cl_2 and 30 mL of 2M aqueous K_2CO_3. The biphasic mixture was stirred vigorously for 6 hours at room temperature. The aqueous phase was separated and extracted twice with CH_2Cl_2. The organic phases were combined, dried over magnesium sulfate and concentrated. The resulting crude product was purified by column chromatography on silica gel eluting with EtOAc. The title compound (1 g, 80%) was obtained as a pale yellow solid.

$C_{10}H_8OClNS$ MS $(M+H)^+$ = 226, Cl pattern

Part E. 2-Chloromethyl -5-(5-chloro-thiophen-2-yl)-pyridine hydrochloride

A solution of 5-(5-Chloro-thiophen-2-yl)-2-hydroxymethyl-pyridine (550 mg, 2.44 mmol) in 20 mL of thionyl chloride was refluxed for 2 hours and concentrated under vacuum. The resulting solid was washed 3 times with Et_2O and dried under vacuum. The title compound (600 mg, 88%), obtained as a green solid, was used without further purification. $C_{10}H_7ClNS$ MS $(M+H)^+$ = 244, Cl pattern.

Synthesis of 5-Bromomethyl-2-(5-chloro-thiophen-2-yl)-thiazole



Part A. 5-Chlorothiophene-2-carboxamide

To a solution of 5-chlorothiophene-2-carboxylic acid (5 g, 30.75 mmol) in 100 mL of dichloromethane were added oxalyl chloride (3.2 mL, 36.90 mmol) and 10 drops of DMF. After 2 hours at room temperature the solution was concentrated under vacuum and the residue was taken up in 100 mL of THF. A stream of NH_3 was passed through the reaction medium for 10 minutes and the suspension was stirred for 1 h 30. Water was added and the THF was evaporated under vacuum. The solid was filtered, washed with water and cyclohexane, and dried under vacuum. The titled compound (4.7 g, 95%) was obtained as a white solid.
C_5H_4OClNS

Part B. 5-Chlorothiophene-2-thiocarboxamide

5-Chlorothiophene-2-carboxamide (4.24 g, 26.2 mmol) and phosphorus pentasulfide (2.33 g, 5.25 mmol) were mixed in 80 mL of toluene and the reaction mixture was refluxed for 5 hours. After cooling the black solid was removed by filtration. The filtrate was treated with activated charcoal and filtrated again. The yellow solution was dried over magnesium sulfate and concentrat-ed. The resulting crude product was purified by column chromatography on silica gel eluting with Chloroform 95 %/ MeOH 5 %. The title compound (1.71 g, 37%) was obtained as a yellow solid.
$C_5H_4ClNS_2$

Part C. 2-(5-Chloro-thiophen-2-yl)-thiazole-5-carboxylic acid methyl ester

5-Chlorothiophene-2-thiocarboxamide (546 mg, 3.08 mmol) and methylchloroformyl acetate (663 mg at 95% pure, 4.6 mmol) were dissolved in 4.5 mL of methanol and the resulting mixture was refluxed for 3 hours, at which time additional methylchloroformylacetate (288mg at 95% pure, 2 mmol) was added. After refluxing for 20 hours the reaction mixture was concentrated under vacuum. The resulting crude product was purified by column chromatography on silica gel eluting with Cyclohexane 99 %/ EtOAc 1 %. The title compound (203 mg, 25%) was obtained as a white solid. $C_9H_6ClNO_2S_2$

Part D. 2-(5-Chloro-thiophen-2-yl)- 5-hydroxymethyl-thiazole

To a stirred suspension of 2-(5-Chloro-thiophen-2-yl)-thiazole-5-carboxylic acid methyl ester (194 mg, 0.748 mmol) in 12 mL of methanol was added, at room temperature, $NaBH_4$ (300 mg, 7.9 mmol). After 2 hours, additional $NaBH_4$ (300 mg, 7.9 mmol) was added and the reaction mixture was stirred at room temperature for 2 hours. Water was added and the methanol was evaporated under vacuum. The resulting aqueous solution was neutralized with 0.1 N HCl, and extracted with EtOAc; the organic layer was dried over magnesium sulfate and concentrated under vacuum. The title compound (173 mg, 85%) was used without further purification. $C_8H_6ClNOS_2$

Part E. 5-Bromomethyl-2-(5-chloro-thiophen-2-yl)-thiazole

To a solution of 2-(5-Chloro-thiophen-2-yl)- 5-hydroxymethyl-thiazole (90 mg, 0.39 mmol) in 5 mL of CH_2Cl_2 was added at 0 °C triphenylphosphine (122 mg, 0.467 mmol) and *N*-bromosuccinimide (83 mg, 0.467 mg). After stirring for 10 minutes at 0°C the reaction mixture was warmed to room temperature for 30 minutes. The solvent was removed under vacuum and the resulting crude product was purified by column chromatography on silica gel eluting with Cyclohexane 90 %/ AcOEt 10 % to give the title compound (31 mg, 27%). $C_8H_5BrClNS_2$

Using the methylhalides described in the preparations and the methods of the previous examples the following inhibitors were prepared:

Example 1533 1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-pyridin-2-ylmethyl]-piperazin-2-one tritrifluoroacetate

To a solution of 2-Chloromethyl -5-(5-chloro-thiophen-2-yl)-pyridine hydrochloride (600 mg, 2.13 mmol) in 25 mL of DMF was added 1-(4-Amino-quinazolin-7-ylmethyl)-piperazin-2-one (500 mg, 1.94 mmol), followed by *N*-ethyldiisopropylamine (1.5 ml, 8.61 mmol). The mixture was stirred a room temperature for 2 days, diluted with 100 mL of water. After stirring for 1 hour the yellow solid was filtered, washed thoroughly with water and dried under vacuum. The solid was purified by column chromatography on silica gel eluting with CH_2Cl_2 then 10 % MeOH - CH_2Cl_2 followed by RP-HPLC eluting in a mixture of 50% CH_3CN/H_2O (0.1% TFA). The appropriate collected fractions were lyophilized to afford the titled compound as a white solid (467 mg, 29 % yield). $C_{23}H_{21}OClN_6S$ MS $(M+H)^+ = 465$, Cl pattern. NMR (1H, DMSO) 9.82 (d, J = 17 Hz, 2H); 8.90 (d, J = 3 Hz, 1H); 8.82 (s, 1H); 8.41 (d, J = 10 Hz, 1H); 8.12 (dd, J = 2 Hz, J = 9 Hz, 1H); 7.70 (s, 1H); 7.63 (d, J = 9 Hz, 1H); 7.58 (s, 1H); 7.56 (m, 1H); 7.22 (dd, J = 1 Hz, J = 4 Hz, 1H); 4.78 (s, 2H); 4.34 (s, 2H) ; 3.82 (s, 2H); 3.50 (m, 2H); 3.48 (m, 2H).

Using the methylhalides described in the preparations and the methods of the previous examples the following inhibitors were prepared:

Example 1534 1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3-(S)-methoxymethyl-piperazin-2-one ditrifluoroacetate.

^{1}H NMR (300 MHz, DMSO) δ 9.76 (2H, bs), 8.81 (1H, s), 8.37 (1H, d, J = 8.6 Hz), 7.55 - 7.61 (3H, m), 7.27 - 7.29 91H, m), 6.89 (1H, s), 4.80 (1H, d, J = 16.1 Hz), 4.65 (1H, d, J = 16.0 Hz), 4.00 (1H, d, J = 14.6 Hz), 3.78 - 3.83 (4H, m), 3.36 (2H, s), 3.27 (3H, s), 3.06 - 3.10 (1H, m), 2.67 - 2.68 (1H, m). MS (Ion spray) $[M+H]^+$ of 499/501 observed, chloro pattern

Example 1535 1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3-(S)-propyl-piperazin-2-one ditrifluoroacetate.

^{1}H NMR (300 MHz, DMSO) δ 9.74 (2H, bs), 8.81 (1H, s), 8.37 (1H, d, J = 8.5 Hz), 7.54 - 7.61 (3H, m), 7.28 - 7.29 (1H, m), 6.88 (1H, s), 4.64 - 4.76 (2H, m), 3.91 (1H, d, J = 14.4 Hz), 3.71 (1H, d, J = 14.4 Hz), 3.27 - 3.30 (2H, m), 3.13 91H, t, J = 4.7 Hz), 3.01 - 3.05 (1H, m), 2.61 - 2.65 (1H, m), 1.80 - 1.86 (2H, m), 1.39 - 1.52 (1H, m), 1.13 - 1.27 (1H, m), 0.80 - 0.85 (3H, m). MS (Ion spray) $[M+H]^+$ of 497/499 observed, chloro pattern.

Example 1536 1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3-(S)-methyl-piperazin-2-one ditrifluoroacetate.

^{1}H NMR (300 MHz, DMSO) δ 9.76 (2H, bs), 8.81 (1H, s), 8.36 (1H, d, J = 8.6 Hz), 7.59 - 7.61 (2H, m), 7.52 (1H, s), 7.29 (1H, d, J = 4.0 Hz), 6.92 (1H, s), 4.63 - 4.70 (2H, m), 3.95 (1H, d, J = 14.5 Hz), 3.76 (1H, d, J = 14.5 Hz), 3.24 - 3.32 (3H, m), 2.97 - 3.05 (1H, m), 2.60 - 2.70 (1H, m), 1.40 (3H, d, J = 6.8 Hz). MS (Ion spray) $[M+H]^+$ of 469/471 observed, chloro pattern.

Example 1537 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]- piperazin-2-one ditrifluoroacetate.

^{1}H NMR (300 MHz, DMSO) δ 9.81 (1H, bs), 9.77 (1H, s), 8.80 (1H, s), 8.38 (1H, d, J = 8.5 Hz), 7.59 - 7.62 (2H, m), 7.24 (1H, d, J = 3.9 Hz), 7.04 (1H, s), 4.71 (2H, s), 3.91(2H, s), 3.30 - 3.34 (4H, m), 2.82 - 2.85 (2H, m). MS (Ion spray) $[M+H]^+$ of 455/457 observed, chloro pattern.

Example 1538 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]-3- methoxymethyl-piperazin-2-one ditrifluoroacetate.

^{1}H NMR (300 MHz, DMSO) δ 9.73 (2H, bs), 8.80 (1H, s), 8.37 (1H, d, J = 8.6 Hz), 7.55 - 7.62 (3H, m), 7.24 - 7.26 (1H, m), 7.00 (1H, s), 4.80 (1H, d, J = 16.2 Hz), 4.65 (1H, d, J = 16.0 Hz),

4.10 (1H, d, J = 15.6 Hz), 3.98 (1H, d, J = 15.6 Hz), 3.78 - 3.86 (3H, m), 3.33 (2H, s), 3.28 (3H, s), 3.10 - 3.14 (1H, m), 2.66 - 2.73 (1H, m). MS (Ion spray) $[M+H]^+$ of 499/501 observed, chloro pattern.

Example 1539 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]-3- methyl-piperazin-2-one ditrifluoroacetate.
^{1}H NMR (300 MHz, DMSO) δ 9.76 (2H, bs), 8.81 (1H, s), 8.36 (1H, d, J = 8.6 Hz), 7.59 - 7.62 (2H, m), 7.51 (1H, s), 7.25 (1H, d, J = 3.9 Hz), 7.03 (1H, s), 4.69 (2H, s), 4.05 (1H, d, J = 15.6 Hz), 3.94 (1H, d, J = 15.5 Hz), 3.34 - 3.36 (1H, m), 3.20 - 3.26 (2H, m), 3.04 - 3.08 (1H, m), 2.65 - 2.71 (1H, m), 1.40 (3H, d, J = 6.8 Hz). MS (Ion spray) $[M+H]^+$ of 469/471 observed, chloro pattern

Example 1540 1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-2H-pyrazol-3-ylmethyl]- piperazin-2-one ditrifluoroacetate.
^{1}H NMR (300 MHz, DMSO) δ 9.81 (1H, s), 9.77 (1H, s), 8.80 (1H, s), 8.36 (1H, d, J = 8.6 Hz), 7.58 - 7.62 (2H, m), 7.26 (1H, d, J = 3.9 Hz), 7.10 (1H, d, J = 3.9 Hz), 6.62 (1H, s), 4.73 (2H, s), 3.95 (2H, s), 3.50 (2H, s), 3.38 (2H, s), 3.02 (2H, s). MS (Ion spray) $[M+H]^+$ of 454/456 observed, chloro pattern

Example 1541 1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-2H-pyrazol-3-ylmethyl]-3-(S)-methyl-piperazin-2-one ditrifluoroacetate.
^{1}H NMR (300 MHz, DMSO) δ 9.76 (2H, bs), 8.81 (1H, s), 8.36 (1H, d, J = 8.6 Hz), 7.60 (1H, d, J = 8.6 Hz), 7.54 (1H, s), 7.25 (1H, d, J = 3.9 Hz), 7.09 (1H, d, J = 3.9 Hz), 6.61 (1H, s), 4.64 - 4.77 (2H, m), 3.98 - 4.10 (1H, m), 3.79 - 3.92(1H, m), 3.25 - 3.46 (3H, m), 3.09 - 3.20 (1H, m), 2.70 - 2.85 (1H, m), 1.47 (3H, d, J = 6.6 Hz). MS (Ion spray) $[M+H]^+$ of 468/470 observed, chloro pattern.

Example 1542 1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-2H-pyrazol-3-ylmethyl]-3-(S)-methoxymethyl-piperazin-2-one ditrifluoroacetate)
^{1}H NMR (300 MHz, DMSO) δ 9.73 (2H, bs), 8.80 (1H, s), 8.36 (1H, d, J = 8.6 Hz), 7.60 (1H, d, J = 8.6 Hz), 7.54 (1H, s), 7.23 (1H, d, J = 3.9 Hz), 7.07 (1H, d, J = 3.9 Hz), 6.56 (1H, s), 4.81 (1H, d, J = 16.1 Hz), 4.64 (1H, d, J = 16.1 Hz), 3.65 - 4.00 (5H, m), 3.26 - 3.38 (5H, m), 3.04 - 3.16 (1H, m), 2.55 - 2.64 (1H, m). MS (Ion spray) $[M+H]^+$ of 498/500 observed, chloro pattern.

Example 1543 1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(3-chloro-phenyl)-4H-[1,2,4]triazol-3-ylmethyl]-(s)-3-methoxymethyl-piperazin-2-one ditrifluorocetate.
^{1}HNMR: (DMSO-d6) 9.79(s, 2H), 8.80 (s, H), 8.37 (d, H), 8.04 (s, H), 7.95 (m, H), 7.47-7.68 (m, 4H), 4.57-5.94 (m, 4H), 4.40 (s, H), 4.11 (m, 2H), 3.42-3.84 (m, 4H), 3.37 (s, 3H). MS: (M+H), 493, 495.

Example 1544 1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(3-chloro-phenyl)-4H-[1,2,4]triazol-3-ylmethyl]-piperazin-2-one ditrifluorocetate.
^{1}HNMR: (DMSO-d6) 9.80(s, 2H), 8.79 (s, H), 8.36 (d, H), 8.00 (s, H), 7.91 (s, H), 7.43- 7.68 (d, H), 4.75 (m, 5H), 4.05-4.83 (m, 4H), 3.10-4.02 (m, 6H). MS: (M+H), 449, 451.

Example 1545 1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl)-4H-[1,2,4]triazol-3-ylmethyl]-piperazin-2-one ditrifluorocetate.
^{1}HNMR: (DMSO-d6) 9.81(s, 2H, NH2), 8.80 (s, H), 8.36 (d, H), 7.65 (s, H), 7.58 (d, H), 7.56 (d, 4H), 7.14 (d, H), 4.75 (s, 2H), 4.54 (s, 2H), 4.04 (s, 2H), 3.43-3.70 (m, 4H). MS: (M+H), 455, 457

Example 1546 1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl)-4H-[1,2,4]triazol-3-ylmethyl]-(s)-3-methoxymethyl-piperazin-2-one ditrifluorocetate.
^{1}HNMR: (DMSO-d6) 9.79(s, 2H, NH2), 8.76 (s, H), 8.37 (d, H), 7.63 (s, H), 7.57 (d, H), 7.54 (d, H), 7.18 (d, H), 4.52-4.94 (m, 4H), 4.34 (s, 2H), 4.03 (m, 2H), 3.45-3.80 (m, 4H), 3.37 (s, 3H). . MS: (M+H), 499, 501.

Example 1547 1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(4-chloro-phenyl)-4H-[1,2,4]triazol-3-ylmethyl]-(s)-3-methoxymethyl-piperazin-2-one ditrifluorocetate.
^{1}HNMR: (DMSO-d6) 9.78(s, 2H, NH2), 8.77 (s, H), 8.35 (d, H), 8.00 (d, H), 7.61 (s, H), 7.52 (m, 3H), 4.57-5.93 (m, 4H), 4.38 (m, H), 4.10 (m, 2H), 3.45-3.84 (m, 4H), 3.39 (s, 3H). MS: (M+H), 493, 495.

Example 1548 1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl-[1,3,4]oxadiazol-2-ylmethyl]-(s)-3-methyl-piperazin-2-one ditrifluorocetate.
^{1}HNMR: (DMSO-d6) 9.76 (d, 2H, NH2), 8.75 (s, H), 8.35 (d, H), 7.64 (d, H), 7.57 (d, H), 7.55 (s, H), 7.25 (d, H), 4.43-4.80 (m, 4H), 4.72-3.84 (m, H), 3.10-3.55 (m, 4H), 1.55 (d, 3H). . MS: (M+H), 470, 472.

Example 1549 1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl)-4H-[1,2,4]triazol-3-ylmethyl]-(s)-3-methyl-piperazin-2-one ditrifluorocetate.
^{1}HNMR: (DMSO-d6) 9.78(d, 2H, NH2), 8.85 (s, H), 8.36 (d, H), 8.01 (s, H, NH), 7.94 (d, H), 7.63 (s, H), 7.60 (d, H), 7.54 (d, H), 4.50-4.86 (m, 4H), 4.22 (m, H), 3.40-3.84 (m, 4H), 1.68 (d, 3H). . MS: (M+H), 463, 465.

Example 1550 1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl)-4H-[1,2,4]triazol-3-ylmethyl]-(s)-3-methoxymethyl-piperazin-2-one ditrifluorocetate.
^{1}HNMR: (DMSO-d6) 9.76(s, 2H, NH2), 8.76 (s, H), 8.36 (d, H), 7.65 (d, H), 7.59 (s, H), 7.57 (d, H), 7.26 (d, H), 5.74 (q, 2H), 4.35-4.55 (m, 3H), 3.00-4.00 (m, 9H including s, 3H). MS: (M+H), 500, 502.

Example 1551 1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl-[1,3,4]oxadiazol-2-ylmethyl]-piperazin-2-one ditrifluorocetate.
^{1}HNMR: (DMSO-d6) 9.78(d, 2H, NH2), 8.79 (s, H), 8.35 (s, H), 7.66 (d, H), 7.63 (s, H), 7.56 (d, H), 7.29 (d, H), 4.72 (s, 2H), 4.56 (s, 2H), 3.85 (s, 2H), 3.32-3.52 (d, 4H) . MS: (M+H), 456, 458.

Example 1552 1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(4-chloro-phenyl)-4H-[1,2,4]triazol-3-yl-methyl]-piperazin-2-one ditrifluorocetate.
^{1}HNMR: (DMSO-d6) 9.80(d, 2H, NH2), 8.78 (s, H), 8.37 (d, H), 8.00 (d, 2H), 7.66 (s, H), 7.60 (d, H), 7.56 (d, 2H), 4.78 (s, 2H), 4.60 (s, 2H), 4.10 (s, 2H), 3.45-3.72 (m, 4H), MS: (M+H), 449, 451.

Example 1553 1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl-[1,3,4]thiadiazol-2-ylmethyl]-piperazin-2-one ditrifluorocetate.
^{1}HNMR: (DMSO-d6) 9.80 (d, 2H, NH2), 8.79 (s, H), 8.36 (d, H), 7.72 (d, H), 7.64 (s, H), 7.60 (d, H), 7.22 (d, H), 4.53-5.87 (m, 4H), 4.80-4.96 (m, 2H), 3.31-3.64 (m, 4H) . MS: (M+H), 472, 474.

Example 1554 1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl)-[1,3,4]thiadiazol-3-ylmethyl]-(s)-3-methoxymethyl-piperazin-2-one ditrifluorocetate.
^{1}HNMR: (DMSO-d6) 9.77 (s, 2H, NH2), 8.79 (s, H), 8.37 (d, H), 7.66 (d, H), 7.60 (d, H), 7.58 (s, H), 7.22 (d, H), 4.52-4.87 (m, 5H), 3.94-4.00 m, 9H). MS: (M+H), 516, 518

Example 1555 1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl)-[1,3,4]thiadiazol-3-ylmethyl]-(s)-3-methyl-piperazin-2-one ditrifluorocetate.
^{1}HNMR: (DMSO-d6) 9.78 (d, 2H, NH2), 8.81 (s, H), 8.37 (d, H), 7.68(d, H), 7.60 (d, H), 7.68 (s, H), 7.21 (d, H), 4.50-4.85 (m, 5H), 3.10-3.90 (m, 4H)., 1.52 (d, 3H). MS: (M+H), 486, 488.

Example 1556 1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl)-[1,3,4]thiadiazol-3-ylmethyl]-(s)-3-propyl-piperazin-2-one ditrifluorocetate.
1HNMR: (DMSO-d6) 9.74 (s, 2H, NH2), 8.79 (s, H), 8.36 (d, H), 7.62 (d, H), 7.57 (d,H), 7.55 (s, H), 7.16 (d, H), 4.58-4.83 (m, 3H), 4.40 (q, 2H), 2.80-3.53 (m, 4H), 1.67-2.00 (m, 2H), 1.15-1.60 (m, 2H), 0.85 (t, 3H). MS: (M+H), 514, 516.

Example 1557 1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl)-[1,3,4]thiadiazol-3-ylmethyl]-(s)-3-ethyl-piperazin-2-one ditrifluorocetate.
1HNMR: (DMSO-d6) 9.85 (s, 2H, NH2), 8.80 (s, H), 8.38 (d, H), 7.66 (d, H), 7.64 (d, H), 7.56 (s, H), 7.17 (d, H), 4.75 (m, 3H), 4.35 (q, 2H), 2.80-3.45 (m, 4H), 1.80-1.12 (m, 2H), 0.88 (t, 3H). MS: (M+H), 500, 502.

Example 1558 1-4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]- piperazin-2-one ditrifluoroacetate.
^{1}H NMR (300 MHz, DMSO) δ 9.75 (2H, bs), 8.81 (1H, s), 8.36 (1H, d, J = 8.6 Hz), 7.55 - 7.63 (3H, m), 7.29 (1H, d, J = 4.0 Hz), 6.92 (1H, s), 4.71 (2H, s), 3.74 (2H, s), 3.18 - 3.29 (4H, m), 2.76 - 2.78 (2H, m). MS (Ion spray) $[M+H]^+$ of 455/457 observed, chloro pattern.

Example 1559 1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-pyridin-5-yl-methyl]-piperazin-2-one tritrifluoroacetate
Part A. 2-Bromo-5-pyridinecarboxaldehyde
To a solution of 2,5-dibromopyridine (1g, 4.22 mmol) in 10 mL of THF was added dropwise at -78 °C *n*-BuLi (1.7 mL, 2.5 N solution in hexane, 4.25 mmol). After 15 minutes at this temperature DMF (0.49 mL, 6.33 mmol) was added and the reaction mixture was stirred for 15 minutes. Methanol was added and the solution was diluted with AcOEt, washed with water, brine, dried over magnesium sulfate and concentrated. The resulting crude product was purified by column chromatography on silica gel eluting with heptane90 %/ AcOEt 10% then heptane 85%/AcOEt 15%. The title compound (146 mg, 18%) was obtained as a yellow solid. C_5H_4OBrN MS $(M+H)^+$ = 185, Br pattern
Part B. 2-(5-Chloro-thiophen-2-yl)-5-pyridinecarboxaldehyde

To a solution of 2-Bromo-5-pyridinecarboxaldehyde (140 mg, 0.756 mmol) in 5 mL of DME was added 5-chlorothiophene-2-boronic acid (131 mg, 0.806 mmol), tetrakis(triphenyl-phosphine) palladium(0) (47 mg, 0.041 mmol) and Na_2CO_3 (0.7 mL of 2 M aqueous solution) under nitrogen. The mixture was refluxed for 5 hours, concentrated under vacuum, taken-up in AcOEt. The solution was washed with water, brine, dried over magnesium sulfate and concentrated. The resulting crude product was purified by column chromatography on silica gel eluting with heptane 95 %/ AcOEt 5% then heptane 90%/AcOEt 10%. The title compound (137 mg, 81%) was obtained as a yellow solid. $C_{10}H_6OClNS$ MS $(M+H)^+$ = 224, Cl pattern

Part C. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-pyridin-5-ylmethyl]-piperazin-2-one tritrifluoroacetate

To 1-(4-Amino-quinazolin-7-ylmethyl)-piperazin-2-one (20 mg, 0.078 mmol) in 5 mL of acetonitrile is added 2-(5-Chloro-thiophen-2-yl)-5-pyridinecarboxaldehyde (17 mg, 0.078 mmol), sodiumtriacetoxyborohydride (33 mg, 0.156 mmol) and 2mL of AcOH. The mixture was stirred at room temperature overnight, then diluted with EtOAc, washed with a saturated aqueous $NaHCO_3$ solution, brine, died over magnesium sulfate and concentrated. The product was purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O(0.1% TFA) to 80% CH_3CN/H_2O(0.1% TFA). The appropriate collected fractions were lyophilized to afford the titled compound as a white solid (2 mg, 3 % yield). $C_{23}H_{21}OClN_6S$ MS $(M+H)^+$ = 465, Cl pattern

Example 1560 4-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one ditrifluoroacetate

To a solution of 2-(2-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (0.33g, 1.0 mmol) and Et_3N (0.34 mL, 2.4 mmol) in MeCN (40 mL) was added a solution of 3-bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole in MeCN (10 mL). The solution was stirred at r.t. overnight and concentrated to dryness. The residue was then treated with 20% TFA/DCM (40 mL) overnight. The solution was concentrated. The residue was purified by RP HPLC to give the product as a white solid (0.23 g, 0.35 mmol). ^1H NMR (DMSO) δ 14.6 (br, 1H), 12.7 (s, 1H), 9.14 (s, 1H), 8.36 (d, 1H), 7.86 (d, 1H), 7.61 (d, 1H), 7.33 (d, 1H), 6.93 (s, 1H), 6.87 (s, 1H), 4.75 (s, 2H), 3.75 (s, 2H), 3.36 (t, 2H), 3.23 (s, 2H), 2.75 (t, 2H). MS M+1: 428, 430.

Example 1561 4-[5-(5-Chloro-thiophen-2-yl)-4H-[1,2,4]triazol-3-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one ditrifluoroacetate

The title compound was similarly prepared from 2-(2-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester and 3-bromomethyl-5-(5-chloro-thiophen-2-yl)-

[1,2,4]triazole-4-carboxylic acid tert-butyl ester. ^{1}H NMR (DMSO) δ 14.6 (br, 1H), 12.68 (s, 1H), 9.20 (s, 1H), 8.36 (d, 1H), 7.88 (d, 1H), 7.48 (d, 1H), 7.20 (d, 1H), 6.89 (s, 1H), 4.74 (s, 2H), 3.90 (s, 2H), 3.38 (m, 4H), 2.81 (t, 2H). MS M+1: 428, 430.

Example 1562 [5-(5-Chloro-thiophen-2-yl)-[1,3,4]oxadiazol-2-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one

The title compound was similarly prepared from 2-(2-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester and 2-bromomethyl-5-(5-chloro-thiophen-2-yl)-[1,3,4]oxadiazole. ^{1}H NMR (DMSO) δ 14.6 (br, 1H), 12.67 (s, 1H), 9.19 (s, 1H), 8.36 (d, 1H), 7.86 (d, 1H), 7.69 (d, 1H), 7.32 (d, 1H), 6.88 (s, 1H), 4.75 (s, 2H), 4.01 (s, 2H), 3.35 (s, 2H), 3.14 (m, 4H), 2.85 (t, 2H). MS M+1: 429, 431.

Example 1563 4-[5-(5-Chloro-thiophen-2-yl)-oxazol-2-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one ditrifluoroacetate

The title compound was similarly prepared from 2-(2-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester and 2-Bromomethyl-5-(5-chloro-thiophen-2-yl)-oxazole. ^{1}H NMR (DMSO) δ 14.6 (br, 1H), 12.7 (s, 1H), 9.16 (s, 1H), 8.36 (d, 1H), 7.86 (d, 1H), 7.49 (s, 1H), 7.30 (d, 1H), 7.20 (d, 1H), 6.87 (s, 1H), 4.74 (s, 2H), 3.79 (s, 2H), 3.30 (t, 2H), 3.25 (s, 2H), 2.89 (t, 2H). MS M+1: 428, 430.

Example 1564 4-[5-(5-Chloro-thiophen-2-yl)-[1,3,4]thiadiazol-2-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one ditrifluoroacetate

The title compound was similarly prepared from 2-(2-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester and 2-bromomethyl-5-(5-chloro-thiophen-2-yl)-[1,3,4]thiadiazole. ^{1}H NMR (DMSO) δ 14.5 (br, 1H), 12.7 (s, 1H), 9.18 (s, 1H), 8.37 (d, 1H), 7.87 (d, 1H), 7.69 (d, 1H), 7.26 (d, 1H), 6.87 (s, 1H), 4.75 (s, 2H), 4.05 (s, 2H), 3.33 (t, 2H), 3.14 (s, 2H), 2.80 (t, 2H). MS M+1: 445, 447.

Example 1565 4-[5-(5-Chloro-thiophen-2-yl)-2H-pyrazol-3-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one ditrifluoroacetate

The title compound was similarly prepared from 2-(2-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester and 5-chloromethyl-3-(5-chloro-thiophen-2-yl)-1H-pyrazole. ^{1}H NMR (CD_3OD) δ 8.71 (s, 1H), 8.10 (d, 1H), 7.37 (d, 1H), 7.13 (d, 1H), 6.93 (d, 1H), 6.55 (s, 1H), 6.48 (s, 1H), 4.75 (s, 2H), 3.69 (s, 2H), 3.37 (t, 2H), 3.24 (s, 2H), 2.72 (t, 2H). MS M+1: 427, 429.

Example 1566 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one ditrifluoroacetate

Part A. 2-(3-Oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

To a solution of piperazin-2-one (2.5 g, 25 mmol) and DIEA (5.2 mL, 30 mmol) in MeCN (50 mL) was added slowly propargyl bromide (4.5 g, 80% in toluene). The solution was stirred at r.t. overnight. The white solid was filtered off and the filtrate was concentrated to residue. The above residue was mixed with (3-iodo-pyridin-4-yl)-carbamic acid tert-butyl ester (6.4 g, 20 mmol), $Pd(PPh_3)_4Cl_2$ (0.70 g, 1 mmol), CuI (0.12 g, 0.6 mmol), Et_3N (14 mL, 100 mmol) in DMF (100 mL). The mixture was heated at 100 °C for 1.5 h, then cooled to 50 °C. DBU (7.5 mL, 50 mmol) was added. The mixture was stirred at 50 °C for another 1.5 h before being concentrated to residue. The residue was treated with activated carbon in CH_2Cl_2 and washed with H_2O. Crude product from CH_2Cl_2 layer was purified by flash column eluting with 5-6% MeOH/CH_2Cl_2 to give off-white foam (1.1 g, 3.3 mmol). ^1H NMR ($CDCl_3$) δ 8.80 (s, 1H), 8.20 (d, 1H), 7.86 (d, 1H), 6.64 (s, 1H), 6.02 (s, 1H), 3.98 (s, 2H), 3.38 (m, 2H), 2.77 (t, 2H). MS M+1: 331.

Part B. 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one ditrifluoroacetate.

A solution of 2-(3-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (0.066 g, 0.20 mmol) in THF (5 mL) was treated NaH (0.010 g, 60%, 0,24 mmol) for 15 min. Bu_4NI was added and the mixture was stirred for another 15 min. 3-Bromomethyl-5-(5-chloro-thiophen-2-yl)-isoxazole (0.056 g, 0.20 mmol) was then added. The mixture was stirred at r.t. for 4 h and concentrated to residue. The residue was then treated with 20% TFA/DCM (4 mL) for 4h and concentrated again. The residue was purified by RP HPLC to give the title compound as a white solid (0.0033 g, 0.005 mmol). ^1H NMR (DMSO) δ 14.5 (br, 1H), 12.8 (s, 1H), 9.20 (s, 1H), 8.37 (d, 1H), 7.84 (d, 1H), 7.62 (d, 1H), 7.28 (d, 1H), 6.94 (s, 1H), 6.80 (s, 1H), 4.57 (s, 2H), 3.86 (s, 2H), 3.3 (m, 2H), 3.19 (s, 2H), 2.74 (m, 2H). MS M+1: 428, 430.

Example 1567 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-(R)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

A 2-Carbomethoxy-6-chlorobenzo[b]thiophene.

To a solution of 4-chloro-2-nitrobenzaldehyde (18 g, 97 mmol) in DMF (100 mL) was added powdered K_2CO_3 (16 g, 116 mmol) followed by methylthioglycolate (8.7 mL, 97 mmol). The mixture was heated to 75 °C for 2 h then cooled to RT and poured into water (2L) The resulting yellow precipitate was collected and dried to yield the title compound (21 g, 93 mmol). Note

that the product can be recrystallized from EtOH/water. ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.03 (s, 1H), 7.85 (s, 1H), 7.80 (d, 1H), 7.39 (d, 1H), 3.95 (s, 3H).

B. 2-Carboxy-6-chlorobenzo[b]thiophene.

5N NaOH (50 mL) was added to a solution of 2-carbomethoxy-6-chlorobenzo[b]thiophene (12.57 g, 55.45 mmol) in MeOH (30 mL) and then heated to 80 °C for 4 h. The reaction mixture was then cooled and made acidic to pH ~3 with concentrated HCl. The resulting precipitate was washed with water then dried under vacuum at 50 °C with P_2O_5 to yield the title compound (11.52 g, 54.18 mmol). ^{1}H NMR (DMSO-d_6, 300MHz) δ 8.21 (s, 1H), 8.11 (s, 1H), 8.00 (d, 1H), 7.50 (d, 1H).

C. 6-Chlorobenzo[b]thiophene.

Copper (5.58 g, 87.9 mmol) was added to a solution of 2-carboxy-6-chlorobenzo[b]thiophene (17.8 g, 83.7 mmol) in quinoline (70 mL) and heated to 180 °C for 1.5 hr. The reaction mixture was then cooled to RT and poured into 500 g of ice. After the ice melted, the mixture was filtered through Celite and the aqueous filtrate acidified with conc. HCl. The aqueous solution was extracted with Et_2O (x3) and the combined ethereal layers were washed with 2N HCl and then brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. The resulting crude product was chromatographic using 50% EtOAc/hexanes to give the title compound (12.48 g, 74.30 mmol). ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.88 (s, 1H), 7.72 (d, 1H), 7.43 (d, 1H), 7.35 (dd, 1H), 7.31 (dd, 1H).

D. 6-Chlorobenzo[b]thiophene-2-sulfonyl chloride.

To a solution of 6-chlorobenzo[b]thiophene (12.5 g, 74.4 mmol) in 250 mL of THF at -78°C was added n-BuLi (29.7 mL of a 2.5M solution in hexanes, 74.4 mmol). After 1h, SO_2 was added dropwise to the solution via a dry-ice condenser. After addition over a one hour period, the solution was stirred for 1 hr then allowed to warm to ambient temperature overnight. The reaction mixture was concentrated and the residue suspended in hexanes (500 mL) and cooled to 0°C. To the solution was added SO_2Cl_2 (7.2 mL, 89.3 mmol) and the resulting suspension was brought to room temperature and stirred for 4 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in EtOAc. The organic solution was washed with saturated $NaHCO_3$ (aq.) and saturated NaCl (aq.). The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude product can be purified by column chromatography eluting with hexanes to yield the title compound as a white solid (18.3 g, 70.3 mmol). ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.11 (s, 1H), 7.88 (m, 2H), 7.50 (m, 1H).

E. 3-Iodopyridin-4ylamine.

A solution of potassium iodide (19.48 g, 117.4 mmol) and iodine (18.37 g, 72.3 mmol) in water (77 mL) was added dropwise via an addition funnel to a refluxing solution of 4-

aminopyridine (9.21 g, 97.8 mmol) and sodium carbonate (6.12 g, 57.7 mmol) in water (35 mL). Upon complete addition the mixture was stirred for 2 hours at reflux then cooled to room temperature and extracted with ethyl acetate. The combined organic layers were washed with saturated sodium thiosulfate solution (3x) and brine then dried over $MgSO_4$, filtered and concentrated to give the title product (8.37 g, 38.0 mmol) and a trace of the di-iodo compound as an yellow/orange solid. This material was used in the subsequent step without further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.70 (s, 1H), 8.10 (d, 1H), 6.55 (d, 1H), 4.60 (bs, 2H).

F. (3-Iodopyridin-4-yl)-carbamic acid tert-butyl ester.

Di-tert-butyl dicarbonate (20.7 g, 94.8 mmol) was added to a solution of 3-iodopyridin-4-ylamine (19.0 g, 86.4 mmol) in THF (86 mL). The resulting solution was stirred for 2 h at room temperature then concentrated. The residue was diluted with ethyl acetate and washed with saturated sodium bicarbonate solution and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography eluting with 1% EtOAc/CH_2Cl_2 to give the title product and a small amount of the BOC-protected di-iodo compound. Trituration of the mixture with ether/hexane removed the undesired compound leaving the title product in solution. Filtration of the solid and concentration of the filtrate yielded the title product (18.95 g, 59.2 mmol). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.75 (s, 1H), 8.35 (d, 1H), 8.1 (d, 1H), 7.05 (bs, 1H), 1.55 (s, 9H).

Alternatively (3-iodopyridin-4-yl)-carbamic acid tert-butyl ester can be made as follows:

G. Pyridin-4-yl-carbamic acid tert-butyl ester.

Di-tert-butyl dicarbonate (43.3 g, 0.20 mmol) was added portionwise to a solution of 4-aminopyridine (18.68 g, 0.20 mol) in THF (300 mL) at room temperature. After 3h, the reaction mixture was concentrated in vacuo and the residue was purified by chromatography using EtOAc as the eluent to yield a white solid as the title compound (38.7 g, 0.20 mmol). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.40 (d, 2H), 7.40 (d, 2H), 6.65 (bs, 1H), 1.5 (s, 9H).

H. (3-Iodopyridin-4-yl)-carbamic acid tert-butyl ester.

nBuLi (255.2 mL of a 2.5M solution in hexanes, 0.64 mol) was added to a solution of xxx (38.7 g, 0.20 mol) and TMEDA (95 mL, 0.64 mol) in THF (400 mL) at -78 °C. After addition the reaction mixture was warmed to -20 °C and stirred for 1.5 h. The mixture was then cooled again to -78 °C and a solution of I_2 (81 g, 0.32 mol) in THF (100 mL) was added dropwise to the reaction vessel. After addition was complete, the resulting solution was brought to room temperature and stirred for 1 h. The reaction mixture was treated with water and then poured into EtOAc. The organic layer was washed with water, saturated sodium thiosulfate (x2) and brine then dried over $MgSO_4$, filtered and concentrated. The crude solid was purified by chromatography using 20% EtOAc/hexanes as the eluent to afford the title compound (58 g,

0.18 mol) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.75 (s, 1H), 8.35 (d, 1H), 8.1 (d, 1H), 7.05 (bs, 1H), 1.55 (s, 9H).

I. 4-[(Methoxycarbonylmethyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester.

Charged 4-oxazolidine aldehyde (75 g, 0.33 mol), glycine methylester hydrochloride (166.25 g. 1.32 mol) and anhydrous methanol (915 mL) to a 2 L 3-necked flask under nitrogen and cooled to 5 °C in an ice water bath. After 30 min a 1M solution of $NaBH_3CN$ in THF (381 ml, 0.38 mol) was added via addition funnel over 10 min. The temperature of the reaction rose to 8 °C during this addition. The reaction was allowed to warm to 23 °C. After 3 h at 23 °C TLC (2 : 1, heptane : EtOAc) showed the reaction to be complete. The solvent was removed under reduced pressure to obtain an oily white solid. MTBE (500 mL) and saturated aqueous sodium bicarbonate was added to the solid and stirred until all solids had dissolved. The phases were allowed to separate and the MTBE layer removed. The aqeous phase was extracted with another 200 mL of MTBE. The organic phases were combined washed with water (100 mL), dried over $MgSO_4$ and evaporated under reduced pressure to obtain the title compound as a light yellow oil (90 g, 0.30 mol). MS (ESI) m/z 303 (M^+ + 1, 100); ^{1}H NMR ($CDCl_3$) δ 3.95 (s, 2H), 3.75 (m, 1H), 3.70 (s, 3H), 3.45 (s, 2H), 2.7 (m, 2H), 1.5 (m, 15H).

J. 4-[(Benzyloxycarbonyl-methoxycarbonylmethyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester.

Charged 4-[(methoxycarbonylmethyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (88 g, 0.29 mol), dichloromethane (1.1 L) and triethylamine (38.3 g, 0.38 mol) to a 2 L 3-necked flask under nitrogen. Cooled the solution to 5 °C and added benzylchloro-formate dropwise via an addition funnel. The addition took 30 min and the temperature of the reaction rose to 10 °C. The reaction was run for 1.5 hours at 2-5 °C and 2 h at 20 °C before TLC (2:1, heptane:EtOAc) showed the reaction to be complete. Once complete aqueous NH_4Cl (300 mL) was added to the mixture and the layers were separated. The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure to obtain a cloudy yellow oil. MTBE (100 mL) was added to this oil and the mixture was filtered through a bed of celite. Removal of the solvent under reduced pressure afforded the title compound as a clear yellow oil (128.5 g, 0.29 mol). MS (ESI) m/z 437 (M^+ + 1, 60), 459 (M^+ + Na, 40); ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 5H), 5.15 (d, 2H), 4.00 (m, 5H), 3.75 (d, 2H), 3.65 (d, 2H), 3.25 (m, 1H), 1.5 (m, 15H).

K. [(2-Amino-3-hydroxy-propyl)-benzyloxycarbonyl-amino]-acetic acid methyl ester hydrochloride.

Charged methanol (1.2 L) to a 2 L 3-necked flask. Bubbled anhydrous HCl into the methanol until the temperature stabilized at 55 °C. Cooled the solution to 20 °C and added 4-[(benzyloxy-

carbonyl-methoxycarbonylmethyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (125 g, 0.28 mol). The solution was stirred at 20-23 °C for 15 h. Distilled off 0.9-1 L of solvent under reduced pressure at 25-30 °C. Solids started to precipitate out of the solution upon cooling so 1 L of MTBE was added, the mixture was cooled to 5 °C and filtered to obtain an off white solid. This material was placed in a vacuum oven to dry at 45 °C and 21 in. Hg vacuum. The title compound was obtained as an off white solid (79.3 g, 0.24 mol) after drying. MS (ESI) m/z 297 (M^+ + 1, 100). ^{1}H NMR ($CDCl_3$) δ 8.10 (s, 3H), 7.30 (m, 5H), 5.15 (d, 2H), 4.40 (s, 1H), 4.15 (m, 2H), 3.95 (m, 1H), 3.70 (m, 5H), 3.50 (s, 2H).

L. 3-(R)-Hydroxymethyl-5-oxo-piperazine-1-carboxylic acid benzyl ester.

Charged methanol (790 ml), [(2-amino-3-hydroxy-propyl)-benzyloxycarbonyl-amino]-acetic acid methyl ester (79 g, 0.24 mol), water (79 mL) and K_2CO_3 (99.5 g, 0.72 mol) to a 1 L 3-necked flask. The mixture was stirred at high speed with a mechanical stirrer for 6 h until TLC (2 : 1, heptane : EtOAc) showed the reaction to be complete. Once completed the reaction was diluted with water (600 mL) and extracted with dichloromethane (3 X 800 mL). The combined dichloromethane layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford the title compound as a viscous amber oil (60 g, 0.23 mol). MS (ESI) m/z 265 (M^+ + 1, 70), 306 (M^+ + CH_3CN, 90); ^{1}H NMR ($CDCl_3$) δ 7.65 (d, 1H), 7.30 (s, 5H), 5.15 (s, 2H), 4.4 (s, 1H), 4.15 (dd, 2H), 3.85 (m, 2H), 3.55 (m, 3H), 3.40 (m, 1H).

M. 3-(R)-(tert-Butyl-dimethyl-silanyloxymethyl)-5-oxo-piperazine-1-carboxylic acid benzyl ester.

3-(R)-Hydroxymethyl-5-oxo-piperazine-1-carboxylic acid benzyl ester (17.6 g, 66.7 mmol), imidazole (5.9 g, 86.7 mmol) and *tert*-butyldimethylsilyl chloride (8.2 g, 54.4 mmol) in CH_2Cl_2 (450 mL) were stirred at room temperature for 2 h. The reaction mixture was filtered and the filtrate concentrated *in vacuo* and purified by chromatography eluting with 2% MeOH/CH_2Cl_2 to yield a colorless oil as the title compound (20.6 g, 54.4 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (s, 5H), 6.40 (bs, 1H), 5.13 (s, 2H), 4.30 (d, 1H), 4.01 (d, 1H), 3.78-3.95 (m, 1H), 3.53-3.71 (m, 2H), 3.49 (m, 1H), 3.22 (m, 1H), 0.93 (s, 9H), 0.1 (s, 6H). MS

N. 3-(R)-(*tert*-Butyl-dimethyl-silanyloxymethyl)-5-oxo-4-prop-2-ynyl-piperazine-1-carboxylic acid benzyl ester.

To a solution of 3-(R)-(*tert*-butyl-dimethyl-silanyloxymethyl)-5-oxo-piperazine-1-carboxylic acid benzyl ester (20.6 g, 54.5 mmol) in DMF/THF (50 mL/250 mL) at 0 °C was slowly added NaH (2.29 g, 57.2 mmol). After stirring for 10 min, propargyl bromide (6 mL, 54.5 mmol) was added and the resulting solution stirred for 1 h. The reaction mixture was then warmed to room temperature and after 2 h the reaction was quenched with water and poured into EtOAc. The organic layer was washed with water (x2) and brine then dried over $MgSO_4$, filtered and concentrated. The resulting crude material was chromatographed using 30% EtOAc/hexanes

as the eluent to yield the title product (18.2 g, 43.7 mmol) as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (s, 1H), 5.20 (s, 2H), 4.78 (d, 1H), 4.28-4.45 (m, 2H), 3.90-4.01 (m, 2H), 3.63-3.78 (m, 3H), 3.30 (dd, 1H), 2.28 (m, 1H), 0.90 (s, 9H), 0.05 (s, 6H). MS

O. 3-(R)-Hydroxymethyl-5-oxo-4-prop-2-ynyl-piperazine-1-carboxylic acid benzyl ester.

To a solution of 3-(R)-(*tert*-butyl-dimethyl-silanyloxymethyl)-5-oxo-4-prop-2-ynyl-piperazine-1-carboxylic acid benzyl ester (18.2 g, 43.7 mmol) in THF (300 mL) was added AcOH (2.77 mL, 48.1 mmol) followed by dropwise addition of nBu_4NF (48.1 mL of a 1M solution in THF, 48.1 mmol). After 3 h, the reaction mixture was treated with water and poured into EtOAc. The organic layer was washed with water and brine then dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by chromatography using 5% MeOH/CH_2Cl_2 to yield an oil as the title product (12.5 g, 41.4 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 (s, 5H), 5.18 (bs, 2H), 4.30-4.61 (m, 3H), 3.85-4.01 (m, 2H), 3.70-3.89(m, 2H), 3.50-3.60 (bd, 1H), 3.20-3.40 (bd, 1H), 2.61 (bs, 1H), 2.28 (m, 1H). ESI MS [M+H]+= 303.

P. 3-(R)-Methoxymethyl-5-oxo-4-propyl-2-ynyl-piperazine-1-carboxylic acid benzyl ester.

To a solution of 3-(R)-hydroxymethyl-5-oxo-4-prop-2-ynyl-piperazine-1-carboxylic acid benzyl ester (10g, 33.1 mmol) in THF/DMF (300 mL/80 mL) at 0 °C was added NaH (1.39g, 34.8 mmol). After 5 min, MeI (2.27 mL, 36.4 mmol) was added and the reaction mixture was stirred for 20 min and then warmed to room temperature. The solution was stirred for 2 hr then treated with water and poured into EtOAc. The organic layer was washed with water and brine then dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by chromatography using 30% EtOAc/hexanes to yield a colorless oil as the title product (7.5 g, 23.7 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36 (s, 5H), 5.18 (s, 2H), 4.75 (d, 1H), 4.41 (m, 1H), 4.28 (d, 1H), 3.75-3.95 (m, 3H), 3.51 (bs, 2H), 3.20-3.48 (m, 4H), 2.22 (m, 1H). ESI MS [M+H]+= 317.

Q. 2-(4-Benzyloxycarbonyl-2-(R)-methoxymethyl-6-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid *tert*-butyl ester.

3-(R)-methoxymethyl-5-oxo-4-propyl-2-ynyl-piperazine-1-carboxylic acid benzyl ester (7.2 g, 22.8 mmol), (3-iodopyridin-4-yl)-carbamic acid tert-butyl ester (7.3 g, 22.8 mmol), CuI (0.13 g, 0.68 mmol), $Pd(PPh_3)_2Cl_2$ (0.80 g, 1.14 mmol) and Et_3N (12.7 mL, 91.1 mmol) in DMF (100 mL) were heated at 100 °C for 3 h then cooled to 50 °C. DBU (6.8 mL, 45.6 mmol) was then added and the resulting mixture was stirred for 1 h. The reaction mixture was then cooled to room temperature and poured into EtOAc. The organic layer was washed with water (x2) and brine then dried over $MgSO_4$, filtered and concentrated. The crude product was purified by 100% EtOAc or 2% MeOH/CH_2Cl_2 to afford the title compound (9.0 g, 17.7 mmol) as a foamy pale yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.78 (s, 1H), 8.42 (d, 1H), 7.90 (d, 1H), 7.31-7.39 (m,

5H), 6.38 (s, 1H), 5.04 (AB, 2H), 5.21 (bs, 2H), 4.30 (AB multiplet, 2H), 4.42 (d, 1H), 3.20-3.68 (m, 5H), 1.71 (s, 9H). ESI MS [M+H]+= 509.

R. 2-(2-(R)-Methoxymethyl-6-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid *tert* butyl ester.

A solution of 2-(4-benzyloxycarbonyl-2-(R)-methoxymethyl-6-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid *tert*-butyl ester (9.0 g, 17.7 mmol) in 5% HCO_2H/MeOH (100 mL) was added to wet Pd black (10 g, 94.0 mmol) under Ar. After 30 min during which vigorous bubbling occurs, the mixture was filtered through Celite and the filtrate neutralized with saturated $NaHCO_3$. The volume of the filtrate was reduced in vacuo and the resulting solution was extracted with CH_2Cl_2. The combined organic layers were washed with brine then dried over $MgSO_4$, filtered and concentrated to yield the title product (5.94 g, 15.9 mmol) as a foamy pale yellow solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.78 (s, 1H), 8.41 (d, 1H), 7.88 (d, 1H), 6.45 (s, 1H), 5.02 (AB, 2H), 3.71 (dd, 1H), 3.64 (d, 2H), 3.50-3.58 (m, 2H), 3.30 (dd, 1H), 3.34 (s, 3H), 3.20 (dd, 1H), 1.71 (s, 9H). HRMS measured 375.2013, calcd 375.2027. ESI MS [M+H]+= 375.

S. 2-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-(R)-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-pyrrolo[3,2-c]pyridine-1-carboxylic acid *tert* butyl ester.

2-(2-(R)-Methoxymethyl-6-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid *tert* butyl ester (5.94 g, 15.9 mmol), 6-chlorobenzo[b]thiophene-2-sulfonyl chloride (4.24 g, 15.9 mmol) and Et_3N (2.4 mL, 17.2 mmol) were stirred in CH_3CN (120 mL) at room temperature for 5 h. The reaction mixture was concentrated to dryness then absorbed onto silica gel with CH_2Cl_2 and chromatographed using EtOAc as the eluent to yield a white solid (6.4 g, 10.6 mmol) as the title compound. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.68 (s, 1H), 8.41 (d, 1H), 7.82-7.91 (m, 4H), 7.50 (dd, 1H), 6.25 (s, 1H), 5.01 (AB, 2H), 4.19 (AB, 2H), 3.62-3.72 (m, 4H), 3.38 (s, 3H), 3.02 (d, 1H), 1.70 (s, 9H). ESI MS [M+H]+= 605, 607, Cl pattern.

T. 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-(R)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

HCl(g) was bubbled into EtOAc (300 mL) at 0 °C for 20 min to saturate the solution. 2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-(R)-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-pyrrolo[3,2-c]pyridine-1-carboxylic acid *tert* butyl ester (5.5 g, 9.2 mmol) was then added and the suspension was stirred for 1 h at 0 °C then brought to room temperature. Additional HCl(g) was bubbled into the slurry during which time the reaction flask became warm. MeOH (60 mL) was subsequently added and the solution became clear. After 1 h, analytical RP-HPLC indicated still a significant amount of starting material so HCl(g) was bubbled through the solution for 30 min at room temperature. The reaction mixture was stirred for 10 h then N_2 was bubbled through the solution for 30 min. The mixture was concentrated to dryness and the

resulting crude material was purified by RP-HPLC (Metachem monochrom 10 micron C-18 column) eluting with a gradient of 20-70% CH_3CN/H_2O (HCl, pH=2.8) over 18 min at 70 mL/min and collecting the fractions eluting at ca. 45% CH_3CN/H_2O (HCl, pH=2.8). The appropriate fractions were lypholized to yield the title product as the hydrochloride salt. ^1H NMR ($CDCl_3$, 300 MHz) δ 11.82 (s, 1H), 8.89 (d, 1H), 8.15 (m, 1H), 7.80-7.85 (m, 3H), 7.77 (d, 1H), 7.41 (d, 1H), 6.75 (s, 1H), 4.90 (AB, 2H), 4.01 (AB, 2H), 3.91 (d, 1H), 3.62-3.78 (m, 3H), 3.34 (s, 3H), 3.13 (d, 1H). EI MS, $[M+H]^+$=505, 507, Cl pattern. HRMS measured 505.0730, calcd 505.0765. Anal. ($C_{22}H_{21}N_4O_4S_2Cl.HCl.1.5H_2O$) Calcd: C, 46.53; H, 4.44; N, 9.87. Found: C, 46.28; H, 4.43; N, 9.45. >99% ee (Chiralpak AD eluting with 100% EtOH).

Example 1568 4-(6-Chlorothieno[2,3-b]pyridine-2-sulfonyl)-6-(R)-methoxymethyl-1-(1H-pyrrolo [3,2-c]pyridin-2-ylmethyl)-piperazin-2-one

A. 6-Chlorothieno[2,3,b]pyridine-2-sulfonyl chloride

6-Chlorothieno[2,3,b]pyridine (J. Het. Chem. (1976), 13, 1197) was converted to the title compound by the method Described in Example 1, Part C: ^1H NMR ($CDCl_3$, 300MHz) δ 8.20 (d, 1H), 8.16 (s, 1H), 7.53 (d, 1H). Mass Spec, M+ 267, 269, 271 two Cl pattern.

B. 4-(6-Chlorothieno[2,3,b]pyridine-2-sulfonyl-(R)-6-methoxymethyl-1-(butylcarboxypyrollo-[3,2,c]pyridine-2-ylmethyl)-piperizin-2-one

2-(2-(R)-Methoxymethyl-6-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert butyl ester (500 mg), 6-chlorothieno[2,3,b]pyridine-2-sulfonyl chloride (360 mg) and 19 ml triethylamine in 50 ml acetonitrile was stirred at room temp overnight. The solution was concentrated, partitioned between ethylacetate and 10% Sodium Bicarbonate. The organic solution was washed with water, dried over sodium sulfate, and chromatographed with 2 % methanol / ethylacetate to give 780 mg of the title compound. Mass Spec M+H=606.2, 608.2 (Cl). ^1H NMR CDCl3 8.7 (s,1H), 8.4 (d, 1H), 8.1 (d, 1H), 7.85 (d, 1H), 7.8 (s,1H), 7.5 (d, 1H), 6.25 (s, 1H), 5.4 (d, 1H), 4.8 (d, 1H), 4.3 (d, 1H), 4.1 (d, 1H), 3.6-3.7 (m, 4H), 3.4 (s,3H), 3.05 (d, 1H), 1.7 (s, 9H).

C. 4-(6-Chloro-thieno[2,3-b]pyridine-2-sulfonyl)-6-(R)-methoxymethyl-1-(1H-pyrrolo [3,2-c]pyridin-2-ylmethyl)-piperazin-2-one

4-(6-chlorothieno[2,3,b]pyridine-2-sulfonyl-(R)-6-methoxymethyl-1-(butylcarboxypyrollo-[3,2,c]pyridine-2-ylmethyl)-piperizin-2-one (700 mg) in 50 ml 40% trifluoroacetic acid in methylenechloride was stirred at room temp for 2 hours, concentrated and purified by HPLC to give 560 mg of the title compound. Mass Spec M+H=506.2, 508.2 (Cl); 1H NMR CD3OD 8.9 (s, 1H), 8.4 (d, 1H), 8.3 (d, 1H), 8.0 (d, 1H), 7.8, (d, 1H), 7.6 (d, 1H), 6.9 (s, 1H), 5.1 (d, 1H), 4.7 (d, 1H), 4.2 (d, 1H), 3.9 (d, 1H), 3.5-3.8 (m, 4H), 3.3 (s,3H),3.2 (d,1H), HPLC > 98A%.

The following 6-substituted ketopiperazine compounds are prepared using synthetic procedures described above.

Example	Name	*m/z* [M+H]
1569	4-(5-Chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	488, 490 Cl pattern
1570	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-(S)-isopropyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	503, 505 Cl pattern
1571	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-(S)-isopropyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	479, 481 Cl pattern
1572	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-one	503, 505 Cl pattern
1573	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-(S)- propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-one	479, 481 Cl pattern

The following ketopiperazines are prepared similar to methods described above.

Example	Name	*m/z* [M+H]
1574	4-(5-Chloro-1H-indole-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	444, 446 Cl pattern
1575	4-[3-(5-Chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	428, 430 Cl pattern
1576	4-[4-(5-Chloro-thiophen-2-yl)-benzyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	481, 483 Cl pattern
1577	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-benzyl]-piperazin-2-one	464, 466 Cl pattern
1578	1-(4-Amino-quinazolin-7-ylmethyl)-4-[4-(5-chloro-thiophen-2-yl)-benzyl]-piperazin-2-one	464, 466 Cl pattern

The following compounds are prepared using methods described above with 3-methyl-4-aminopyridine (prepared according to Recueil 1951, *70*, 571-579) as the starting material.

Example	Name	*m/z* [M+H]
1579	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(7-methyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	475, 477 Cl pattern
1580	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-(7-methyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	451, 453 Cl pattern

Inhibition of Factor Xa

The compounds described herein inhibit blood coagulation by virtue of their ability to inhibit the penultimate enzyme in the coagulation cascade, controlling the activity of Factor Xa. Both the activity of free Factor Xa and Factor Xa assembled in the prothrombinase complex (Factor Xa, Factor Va, calcium and phospholipid) are inhibited by compounds of formula 1. The inhibition of the Factor Xa activity is obtained by direct complex formation between the inhibitor and the enzyme and is therefore independent of the plasma co-factor antithrombin III. Effective inhibition of the Factor Xa activity is achieved by administering the compounds either by oral administration, continuous intravenous infusion, bolus intravenous administration or any other parenteral route such that it achieves the desired effect of preventing the activity of Factor Xa induced formation of thrombin from prothrombin.

Anticoagulant therapy is indicated for the treatment and prophylaxis of a variety of thrombotic conditions of both the venous and arterial vasculature. In the arterial system, abnormal thrombus formation is primarily associated with arteries of the coronary, cerebral and peripheral vasculature. The diseases associated with thrombotic occlusion of these vessels principally include acute myocardial infarction (AMI), unstable angina, thromboembolism, acute vessel closure associated with thrombolytic therapy and percutaneous transluminal coronary angioplasty (PTCA), transient ischemic attacks, stroke, intermittent claudication and bypass grafting of the coronary (CABG) or peripheral arteries. Chronic anticoagulant therapy may also be beneficial in preventing the vessel luminal narrowing (restenosis) that often occurs following PTCA and CABG, and in the maintenance of vascular access patency in long-term hemodialysis patients. With respect to the venous vasculature, pathologic thrombus formation frequently occurs in the veins of the lower extremities following abdominal, knee and hip surgery (deep vein thrombosis, DVT). DVT further predisposes the patient to a higher risk of pulmonary thromboembolism. A systemic, disseminated intravascular coagulopathy (DIC) commonly occurs in both vascular systems during septic shock, certain viral infections and cancer. This condition is characterized by a rapid consumption of coagulation factors and their plasma inhibitors resulting in the formation of life-threatening thrombin throughout the microvasculature of several organ systems. The indications discussed above include some, but not all, of the possible clinical situations where anticoagulant therapy is warranted. Those experienced in this field are well aware of the circumstances requiring either acute or chronic prophylactic anticoagulant therapy.

Accumulated experimental evidence has also reflected that prothrombin activation is only one of the biological activities of Factor Xa. EPR-1 (effector cell protease receptor-1,

recognizing Factor Xa), is believed to mediate several of the vascular wall interactions by Factor Xa. It has been shown to be expressed on human umbilical vein endothelial cells, rat smooth muscle cells and platelets(CR McKenzie, et al., Arterioscler Thromb Vasc Biol 16 1285-91 (1996); also F Bono, et al., J Cell Physiol 172 36-43 (1997), AC Nicholson, et al., J Biol Chem 271 28407-13 (1996),J.M. Herbert, et al., J Clin Invest 101993-1000 (1998)). This protease-receptor interaction could mediate not only prothrombinase-catalyzed thrombin generation, but also diverse cellular functions such as cell proliferation, release of PDGF and DNA syntheses. The mitogenic effect of Factor Xa has been reported to be dependent on Factor Xa enzymatic activity (F Bono, et al., J Cell Physiol 172 36-43 (1997), J.M. Herbert, et al., J Clin Invest 101 993-1000 (1998)). TAP for example inhibited the mitogenesis of human and rat cultured vascular smooth muscle cells (F Bono, et al., J Cell Physiol 172 36-43 (1997)). In a study of the rabbit carotid artery air-drying injury model, increased EPR-1 expression is detected after vascular injury. Animals treated with the specific Factor Xa inhibitor, DX-9065a, exhibited less neointimal proliferation. The important regulatory role of Factor Xa in the coagulation process coupled with its mitogenic effects points to Factor Xa's involvement in the formation of thrombin at the luminal surface of the vessel wall and contribution to the atherothrombotic process and abnormal proliferation of vascular cells resulting in restenosis or angiogenesis.

These compounds may be used alone or in combination with other diagnostic, anticoagulant, antiplatelet or fibrinolytic agents. For example adjunctive administration of inhibitors of the activity of Factor Xa with standard heparin, low molecular weight heparin(s), synthetic pentasaccharides, direct thrombin inhibitors (e.g. hirudin, Agratroban (Novastan®), aspirin, fibrinogen receptor antagonists, statins / fibrates streptokinase, urokinase and/or tissue plasminogen activator. The compounds described herein may be administered to treat thrombotic complications in a variety of animals such as primates including humans. Inhibition of factor Xa is useful not only in the anticoagulant therapy of individuals having thrombotic conditions but is useful whenever inhibition of blood coagulation is required such as to prevent coagulation of stored whole blood and to prevent coagulation in other biological samples for testing or storage. Thus, any inhibitor of Factor Xa activity can be added to or contacted with any medium containing or suspected of containing Factor Xa and in which it is desired that blood coagulation be inhibited.

In addition to their use in anticoagulant therapy, Factor Xa inhibitors may find utility in the treatment or prevention of other diseases in which the generation of thrombin has been implicated as playing a physiologic role. For example, thrombin has been proposed to contribute to the morbidity and mortality of such chronic and degenerative diseases as arthritis,

cancer, atherosclerosis and Alzheimer's disease by virtue of its ability to regulate many different cell types through specific cleavage and activation of a cell surface thrombin receptor, mitogenic effects, diverse cellular functions such as cell proliferation, for example, abnormal proliferation of vascular cells resulting in restenosis or angiogenesis, release of PDGF and DNA syntheses. Inhibition of Factor Xa will effectively block thrombin generation and therefore neutralize any physiologic effects of thrombin on various cell types.

According to a further feature of the invention there is provided a method for the treatment of a human or animal patient suffering from, or subject to, a physiological condition which can be ameliorated by the administration of an inhibitor of the Factor Xa activity, for example conditions as hereinbefore described, which comprises the administration to the patient of a therapeutically effective amount of compound of formula I or formula II, or a composition containing a compound of formula I or formula II,. "Effective amount" is meant to describe an amount of compound of the present invention effective in inhibiting the activity of Factor Xa and thus producing the desired therapeutic effect.

The present invention also includes within its scope pharmaceutical formulations which comprise at least one of the compounds of formula I or formula II in association with a pharmaceutically acceptable carrier or coating.

The pharmaceutical compositions can be administered in a suitable formulation to humans and animals by topical or systemic administration, including oral, inhalational, rectal, nasal, buccal, sublingual, vaginal, parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), intracisternal and intraperitoneal. It will be appreciated that the preferred route may vary with for example the condition of the recipient.

The products according to the invention may be presented in forms permitting administration by the most suitable route and the invention also relates to pharmaceutical compositions containing at least one product according to the invention which are suitable for use in human or veterinary medicine. These compositions may be prepared according to the customary methods, using one or more pharmaceutically acceptable adjuvants or excipients. The adjuvants comprise, inter alia, diluents, sterile aqueous media and the various non-toxic organic solvents. The compositions may be presented in the form of tablets, pills, granules, powders, aqueous solutions or suspensions; injectable solutions, elixirs or syrups, and can contain one or more agents chosen from the group comprising sweeteners, flavorings, colorings, or stabilizers in order to obtain pharmaceutically acceptable preparations.

The choice of vehicle and the content of active substance in the vehicle are generally determined in accordance with the solubility and chemical properties of the product, the particular mode of administration and the provisions to be observed in pharmaceutical practice.

For example, excipients such as lactose, sodium citrate, calcium carbonate, dicalcium phosphate and disintegrating agents such as starch, alginic acids and certain complex silicates combined with lubricants such as magnesium stearate, sodium lauryl sulfate and talc may be used for preparing tablets. To prepare a capsule, it is advantageous to use lactose and high molecular weight polyethylene glycols. When aqueous suspensions are used they can contain emulsifying agents or agents which facilitate suspension. Diluents such as sucrose, ethanol, polyethylene glycol, propylene glycol, glycerol and chloroform or mixtures thereof may also be used.

For parenteral administration, emulsions, suspensions or solutions of the products according to the invention in vegetable oil, for example sesame oil, groundnut oil or olive oil, or aqueous-organic solutions such as water and propylene glycol, injectable organic esters such as ethyl oleate, as well as sterile aqueous solutions of the pharmaceutically acceptable salts, are used. The solutions of the salts of the products according to the invention are especially useful for administration by intramuscular or subcutaneous injection. The aqueous solutions, also comprising solutions of the salts in pure distilled water, may be used for intravenous administration with the proviso that their pH is suitably adjusted, that they are judiciously buffered and rendered isotonic with a sufficient quantity of glucose or sodium chloride and that they are sterilized by heating, irradiation or microfiltration.

Suitable compositions containing the compounds of the invention may be prepared by conventional means. For example, compounds of the invention may be dissolved or suspended in a suitable carrier for use in a nebulizer or a suspension or solution aerosol, or may be absorbed or adsorbed onto a suitable solid carrier for use in a dry powder inhaler.

Solid compositions for rectal administration include suppositories formulated in accordance with known methods and containing at least one compound of formula I or formula II.

Actual dosage levels of active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active compound(s) that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration. The selected dosage level will depend upon the activity of the particular compound, the route of administration, the severity of the condition being treated, and the condition and prior medical history of the patient being treated. However, it is within the skill of the art to start doses of the compound at levels lower than required for to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. In the adult, the doses are generally from about 0.01 to about 100, preferably about 0.01 to about 10, mg/kg body weight per day by inhalation, from about 0.01 to about 100, preferably 0.1 to 70,

more especially 0.5 to 10, mg/kg body weight per day by oral administration, and from about 0.01 to about 50, preferably 0.01 to 10, mg/kg body weight per day by intravenous administration. In each particular case, the doses will be determined in accordance with the factors distinctive to the subject to be treated, such as age, weight, general state of health and other characteristics which can influence the efficacy of the medicinal product.

The products according to the invention may be administered as frequently as necessary in order to obtain the desired therapeutic effect. Some patients may respond rapidly to a higher or lower dose and may find much weaker maintenance doses adequate. For other patients, it may be necessary to have long-term treatments at the rate of 1 to 4 doses per day, in accordance with the physiological requirements of each particular patient. Generally, the active product may be administered orally 1 to 4 times per day. It goes without saying that, for other patients, it will be necessary to prescribe not more than one or two doses per day.

Compounds within the scope of the present invention exhibit marked pharmacological activities according to tests described in the literature which tests results are believed to correlate to pharmacological activity in humans and other mammals. The following pharmacological test results are typical characteristics of compounds of the present invention.

Enzyme Assays:

The ability of the compounds in the present invention to act as inhibitors of factor Xa, thrombin, trypsin, tissue-plasminogen activator (t-PA), urokinase-plasminogen activator (u-PA), plasmin and activated protein C is evaluated by determining the concentration of inhibitor which resulted in a 50% loss in enzyme activity (IC50) using purified enzymes.

All enzyme assays are carried out at room temperature in 96-well microtiter plates using a final enzyme concentration of 1 nM. The concentrations of factor Xa and thrombin are determined by active site titration and the concentrations of all other enzymes are based on the protein concentration supplied by the manufacturer. Compounds according to the invention are dissolved in DMSO, diluted with their respective buffers and assayed at a maximal final DMSO concentration of 1.25%. Compound dilutions are added to wells containing buffer and enzyme and pre-equilibrated for between 5 and 30 minutes. The enzyme reactions are initiated by the addition of substrate and the color developed from the hydrolysis of the peptide-p-nitroanilide substrates is monitored continuously for 5 minutes at 405 nm on a Vmax microplate reader (Molecular Devices). Under these conditions, less than 10% of the substrate is utilized in all assays. The initial velocities measured are used to calculate the amount of inhibitor which resulted in a 50% reduction of the control velocity (IC50). The apparent Ki values are then

determined according to the Cheng-Prusoff equation (IC50 = Ki [1+[S]/Km]) assuming competitive inhibition kinetics.

An additional in vitro assay may be used to evaluate the potency of compounds according to the invention in normal human plasma. The activated partial thromboplastin time is a plasma-based clotting assay that relies on the in situ generation of factor Xa, its assembly into the prothrombinase complex and the subsequent generation of thrombin and fibrin which ultimately yields the formation of a clot as the assay endpoint. This assay is currently used clinically to monitor the ex vivo effects of the commonly used anticoagulant drug heparin as well as direct acting antithrombin agents undergoing clinical evaluation. Therefore, activity in this in vitro assay is considered as a surrogate marker for in vivo anticoagulant activity.

Human Plasma Based Clotting Assay:

Activated partial thromboplastin clotting times are determined in duplicate on a MLA Electra 800 instrument. A volume of 100 ml of citrated normal human pooled plasma (George King Biomedical) is added to a cuvette containing 100 ml of a compound according to the invention in Tris/NaCl buffer (pH 7.5) and placed in the instrument. Following a 3 minute warming period the instrument automatically adds 100 ml of activated cephaloplastin reagent (Actin, Dade) followed by 100 ml of 0.035 M $CaCl_2$ to initiate the clotting reaction. Clot formation is determined spectrophotometrically and measured in seconds. Compound potency is quantitated as the concentration required to double a control clotting time measured with human plasma in the absence of the compound according to the invention.

A compound according to the invention may also be evaluated for their in vivo antithrombotic efficacy in two well established animal experimental models of acute vascular thrombosis. A rabbit model of jugular vein thrombosis and a rat model of carotid artery thrombosis are used to demonstrate the antithrombotic activity of these compounds in distinct animal model paradigms of human venous thrombosis and arterial thrombosis, respectively.

Experimental Plazma Protein Binding Assay

Compounds are dissolved into DMSO to prepare a 10 mM stock. Serial dilutions of compounds are made in a buffer containing 0.05M Tris, 0.15M NaCl, 0.1% PEG-8000, PH 7.5. Human FXa and the substrate, Spectrozyme FXa, are prepared in the aforementioned buffer containing human Albumin and fibrinogen at 3.45 mg/ml and 2.3 mg/ml, respectively. The FXa assay is carried out at room temperature in the 96-well microtiter plates with a final enzyme

concentration and substrate concentration of 1nM and 200 μM, respectively. Compound dilutions are added to the wells containing buffer and FXa and preincubated for 30 minutes. The enzyme reactions are initiated by the addition of substrate, Spectrozyme FXa, and the color developed from the release of p-nitroanilide from each chromogenic substrate is monitored continuously for 5 minutes at 405 nm on a Thermomax microtiter plate reader(Molecular Devices, Sunnyvale, CA.). In the final reaction mixture, the concentration of albumin and fibeinogen is 3mg/ml and 2 mg/ml, respectively.Under the experimental conditions, less than 10% of the substrate is consumed in all assays. The initial velocities measured are used to determine the amount of inhibitor required to diminish 50% of the control velocity and defined as IC_{50} of the inhibitor. Assuming the kinetic mechanisms are competitive inhibition, the apparent Ki values are then calculated according to the Cheng-Prusoff equation , $Ki = IC_{50}/(1 + [S]/Km)$

Experimental In Vivo Rabbit Venous Thrombosis Model:

This is a well characterized model of fibrin rich venous thrombosis that is validated in the literature and shown to be sensitive to several anticoagulant drugs including heparin (Antithrombotic Effect of Recombinant Truncated Tissue Factor Pathway Inhibitor (TFPI 1-161) in Experimental Venous Thrombosis-a Comparison with Low Molecular Weight Heparin, J. Holst, B. Lindblad, D. Bergqvist, O. Nordfang, P.B. Ostergaard, J.G.L. Petersen, G. Nielsen and U. Hedner. Thrombosis and Haemostasis, 71, 214-219 (1994). The purpose of utilizing this model is to evaluate the ability of compounds to prevent the formation of venous thrombi (clots) in vivo generated at a site of injury and partial stasis in the jugular vein.

Male and female New Zealand white rabbits weighing 1.5-2 kg are anesthetized with 35 mg/kg of ketamine and 5 mg/kg xylazine in a volume of 1 ml/kg (i.m.). The right jugular vein is cannulated for infusion of anesthetic (ketamine/xylazine 17/2.5 mg/kg/hr at a rate of approximately 0.5 ml/hr) and administration of test substances. The right carotid artery is cannulated for recording arterial blood pressure and collecting blood samples. Body temperature is maintained at 39°C with a GAYMAR T-PUMP. The left external jugular vein is isolated and all side branches along an exposed 2-3 cm of vessel are tied off. The internal jugular vein is cannulated, just above the bifurcation of the common jugular, and the tip of the cannula is advanced just proximal to the common jugular vein. A 1 cm segment of the vein is isolated with non-traumatic vascular clamps and a relative stenosis is formed by tying a ligature around the vein with an 18G needle just below the distal most clamp. This creates a region of reduced flow and partial stasis at the injury site. The isolated segment is gently rinsed with saline 2-3 times via the cannula in the internal jugular. Thereafter the isolated segment is filled

with 0.5 ml of 0.5% polyoxyethylene ether (W-1) for 5 minutes. W-1 is a detergent which disrupts the endothelial cell lining of the segment, thus providing a thrombogenic surface for initiating clot formation. After 5 minutes the W-1 is withdrawn from the segment, and the segment is again gently rinsed with saline 2-3 times. The vascular clamps are then removed, restoring blood flow through this portion of the vessel. Clot formation is allowed to form and grow for 30 minutes after which the vein is cut just below the stenotic ligature and inspected for blood flow (the absence of blood flow is recorded as complete occlusion). The entire isolated segment of vein is then ligated and the formed clot is removed and weighed (wet weight). The effect of test agents on final clot weights is used as the primary end point. Animals are maintained for an additional thirty minutes to obtain a final pharmacodynamic measure of anticoagulation. Drug administration is initiated 15 minutes prior to vascular injury with W-1 and continued through the period of clot formation and maturation. Three blood samples (3 ml ea.) are obtained for evaluation of hemostatic parameters: one just prior to administration of W-1; a second 30 minutes after removal of the vascular clamps and a third at the termination of the experiment. Antithrombotic efficacy is expressed as a reduction in the final clot weight in preparations treated with a compound according to the invention relative to vehicle treated control animals.

Experimental In Vivo Rat Arterial Thrombosis Model:

The antithrombotic efficacy of factor Xa inhibitors against platelet-rich arterial thrombosis may be evaluated using a well characterized rat carotid artery $FeCl_2$-induced thrombosis model (Superior Activity of a Thromboxane Receptor Antagonist as Compared with Aspirin in Rat Models of Arterial and Venous Thrombosis, W.A. Schumacher, C.L. Heran, T.E. Steinbacher, S. Youssef and M.L. Ogletree. Journal of Cardiovascular Pharmacology, 22, 526-533 (1993); Rat Model of Arterial Thrombosis Induced by Ferric Chloride, K.D. Kurtz, B.W. Main, and G.E. Sandusky. Thrombosis Research, 60, 269-280 (1990); The Effect of Thrombin Inhibition in a Rat Arterial Thrombosis Model, R.J. Broersma, L.W. Kutcher and E.F. Heminger. Thrombosis Research 64, 405-412 (1991). This model is widely used to evaluate the antithrombotic potential of a variety of agents including heparin and the direct acting thrombin inhibitors.

Sprague Dawley rats weighing 375-450 g are anesthetized with sodium pentobarbital (50 mg/kg i.p.). Upon reaching an acceptable level of anesthesia, the ventral surface of the neck is shaved and prepared for aseptic surgery. Electrocardiogram electrodes are connected and lead II is monitored throughout the experiment. The right femoral vein and artery are cannulated with PE-50 tubing for administration of a compound according to the invention and for obtaining blood samples and monitoring blood pressure, respectively. A midline incision is

made in the ventral surface of the neck. The trachea is exposed and intubated with PE-240 tubing to ensure airway patency. The right carotid artery is isolated and two 4-0 silk sutures are placed around the vessel to facilitate instrumentation. An electromagnetic flow probe (0.95-1.0 mm lumen) is placed around the vessel to measure blood flow. Distal to the probe a 4x4 mm strip of parafilm is placed under the vessel to isolate it from the surrounding muscle bed. After baseline flow measurements are made, a 2x5 mm strip of filter paper previously saturated in 35% $FeCl_2$ is placed on top of the vessel downstream from the probe for ten minutes and then removed. The $FeCl_2$ is thought to diffuse into the underlying segment of artery and cause deendothelialization resulting in acute thrombus formation. Following application of the $FeCl_2$-soaked filter paper, blood pressure, carotid artery blood flow and heart rate are monitored for an observation period of 60 minutes. Following occlusion of the vessel (defined as the attainment of zero blood flow), or 60 minutes after filter paper application if patency is maintained, the artery is ligated proximal and distal to the area of injury and the vessel is excised. The thrombus is removed and weighed immediately and recorded as the primary end point of the study.

Following surgical instrumentation a control blood sample (B1) is drawn. All blood samples are collected from the arterial catheter and mixed with sodium citrate to prevent clotting. After each blood sample, the catheter is flushed with 0.5 ml of 0.9% saline. A compound according to the invention is administered intravenously (i.v.) starting 5 minutes prior to $FeCl_2$ application. The time between $FeCl_2$ application and the time at which carotid blood flow reached zero is recorded as time to occlusion (TTO). For vessels that did not occlude within 60 minutes, TTO is assigned a value of 60 minutes. Five minutes after application of $FeCl_2$, a second blood sample is drawn (B2). After 10 minutes of $FeCl_2$ exposure, the filter paper is removed from the vessel and the animal is monitored for the remainder of the experiment. Upon reaching zero blood flow blood a third blood sample is drawn (B3) and the clot is removed and weighed. Template bleeding time measurements are performed on the forelimb toe pads at the same time that blood samples are obtained. Coagulation profiles consisting of activated partial thromboplastin time (APTT) and prothrombin time (PT) are performed on all blood samples. In some instances a compound according to the invention may be administered orally. Rats are restrained manually using standard techniques and compounds are administered by intragastric gavage using a 18 gauge curved dosing needle (volume of 5 ml/kg). Fifteen minutes after intragastric dosing, the animal is anesthetized and instrumented as described previously. Experiments are then performed according to the protocol described above.

Experimental Canine intravenous and intragastric dosing experiments.

Beagle dogs (9-13 kg) of either sex are used to evaluate the pharmacodynamic effect of compounds of this invention after intravenous and intragastric dosing. Blood samples for these experiments are obtained via venipuncture of the cephalic vein. After discarding the first 0.5 ml of blood drawn, the control sample of 4.5 ml of blood is drawn into chilled plastic syringes containing 0.5 ml of trisodium citrate. After drug administration, 0.9 ml of blood is obtained at each time point (after discarding the first 0.5 ml of blood) by drawing the sample directly into chilled plastic syringes containing 0.1 ml trisodium citrate.

For the intravenous experiments, compounds are administered in the cephalic vein in the forelimb contralateral to that used for blood sampling. Compounds are dissolved in saline (0.5 ml/kg body weight) and administered as an i.v. bolus. Post-dosing blood samples are obtained at specific time points after dosing.

For the intragastric experiments, Compounds (in 0.5% methyl cellulose and 1 % polysorbate-80, 1 ml/kg dosing volume) are administered via an intragastric feeding tube. A pre-dosing control blood sample is obtained as above and post-dosing samples are obtained at specific time points after dosing.

Coagulation times. Platelet-poor plasma is used for determination of activated partial thromboplastin time (APTT) and prothrombin time (PT), which are measured using a Microsample Coagulation Analyzer (MCA210, Bio Data Corp, Horsham, PA) and Dade® reagents (Thromboplastin-C Plus and Actin® FS Activated PTT reagent, Baxter Diagnostics, Inc., Deerfield, IL).

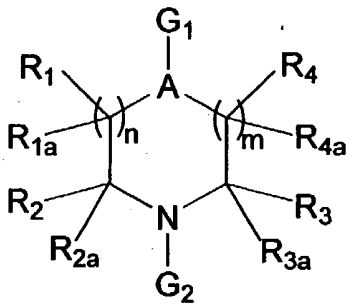
Ex vivo inhibition of Factor Xa. Factor-Xa inhibitory activity is analyzed by chromogenic methods using reagents (bovine factor Xa and spectrozyme Xa) supplied by American Diagnostica (Greenwich, CT). The rate of change of optical density (Vmax, 405 nm) is measured using a SPECTRAmax microtiter plate spectrophotometer and Softmax Pro software (Molecular Devices Corp., Sunnyvale, CA). Inhibition of Xa activity is determined as follows: percent inhibition of Xa activity = 1-(Vmax of sample with inhibitor/Vmax of the pre-drug control sample) X 100.

One skilled in the art will readily appreciate that the present invention is well adapted to carry out the objects of the invention and obtain the ends and advantages mentioned, as well as those inherent therein. The compounds, compositions and methods described herein are presented as representative of the preferred embodiments, or intended to be exemplary and not intended as limitations on the scope of the present invention.

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof.

Claims:

1. A compound of formula I



I

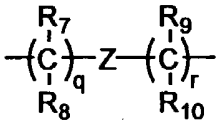
or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof, wherein

G_1 and G_2 are L_1- Cy_1 or L_2- Cy_2, provided that when R_1 and R_{1a} or R_4 and R_{4a} taken together form O or S, then G_1 is L_2- Cy_2 and G_2 is L_1-Cy_1, or when R_2 and R_{2a} or R_3 and R_{3a} taken together form O or S, then G_1 is L_1-Cy_1 and G_2 is L_2-Cy_2;

Cy_1 and Cy_2 are independently selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcycloalkyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylheterocyclyl and optionally substituted fused heteroarylheterocyclenyl;

L_1 is absent, O, NR_5, -S(O)p-, -S(O)pNR_5-, -C(X)Y- or -L_3-Q-L_4-Q'-L_5-, -C(O)Y-C(X)Y-, -C(X)YC(O)-, -C(O)NR_5-S(O)p-, or -C(O)C(O)NR_5S(O)p-;

L_2 is absent or a group of formula



;

L_3 and L_5 are independently absent, optionally substituted alkylene, optionally substituted alkenylene or optionally substituted alkynylene;

L_4 is optionally substituted alkylene, optionally substituted alkenylene, or optionally substituted alkynylene;

Q and Q' are independently absent, O, S, NR_5, -S(O)p-, -S(O)pNR_5- or -C(X)Y-;

A is CH or N;

R_1, R_{1a}, R_2, R_{2a}, R_3, R_{3a}, R_4 and R_{4a} are independently selected from hydrogen, carboxy, alkoxycarbonyl, $Y_1Y_2NC(O)$-, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl, or R_1 and R_{1a}, R_2 and R_{2a}, R_3 and R_{3a}, or R_4 and R_{4a} taken together form O or S; or R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, or heterocyclenyl group; or R_3 and R_4 together with the carbon atoms through which R_3 and R_4 are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, or heterocyclenyl group; or R_{1a} and R_{2a} are absent and R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form an aryl or heteroaryl group; or R_{3a} and R_{4a} are absent and R_3 and R_4 together with the carbon atoms through which R_3 and R_4 are linked form an aryl or heteroaryl group; or one or more of the pairs R_1 and R_{1a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_2 and R_{2a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_3 and R_{3a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group;

or R_4 and R_{4a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group;

m and n are independently 0, 1 or 2, provided that m and n are not both 0 and further provided that when R_1 and R_{1a} taken together form O or S, n is 1, and when R_4 and R_{4a} taken together form O or S, m is 1;

R_5 is hydrogen, optionally substituted alkyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, $R_6O(CH2)v$-, $R_6O2C(CH2)x$-,$Y_1Y_2NC(O)(CH2)x$-, or $Y_1Y_2N(CH2)v$-;

R_6 is hydrogen, optionally substituted alkyl, optionally substituted aralkyl or optionally substituted heteroaralkyl;

Y_1 and Y_2 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted aryl, optionally substituted aralkyl or optionally substituted heteroaralkyl, or Y_1 and Y_2 taken together with the N through which Y_1 and Y_2 are linked form a monocyclic heterocyclyl;

R_7, R_8, R_9 and R_{10} are independently selected from hydrogen, hydroxy, alkoxy, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aralkyl and optionally substituted heteroaralkyl, provided that only one of R_7 and R_8 or one of R_9 and R_{10} is hydroxy or alkoxy, and further provided when any of R_7, R_8, R_9 and R_{10} is hydroxy or alkoxy, then the hydroxy or alkoxy is not α-substituted to an N, O or S in Z;

X is O or S; Y is absent or is selected from O, S and NR_5;

Z is absent or is selected from optionally substituted lower alkenylene, optionally substituted lower alkynylene, O, -C(O)-, S(O)p, NR_5, $-NR_5C(O)-$ and $-C(O)NR_5-$;

x is 1, 2, 3 or 4; v is 2, 3 or 4;

p is 1 or 2; and q and r are independently 0, 1, 2 or 3, provided that q and r are not both 0,

provided that when L_1 is O, NR_5, -S(O)p-, $-S(O)pNR_5-$, -C(X)Y- or $-L_3-Q-L_4-Q'-L_5-$ and R_3 and R_{3a} taken together form O or S, then R_2 and R_{2a} are independently selected from hydrogen, alkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, alkoxyaminoalkyl, cycloalklalkylamino, benzyloxyalkyl, isopropyl, aminomethyl, methoxyethylaminomethyl, piperazin, pyrrolidin, ethoxymethyl, benzyloxymethyl, methoxymethyl, isobutyl, isopropylamino or isopropylaminomethyl, provided that R_2 and R_{2a} are not each hydrogen;

or when L_1 is O, NR_5, -S(O)p-, $-S(O)pNR_5-$, -C(X)Y- or $-L_3-Q-L_4-Q'-L_5-$ and R_3 and R_{3a} taken together form O or S, then R_4 and R_{4a} taken together form O or S;

or when L_1 is O, NR_5, -S(O)p-, $-S(O)pNR_5-$, -C(X)Y- or $-L_3-Q-L_4-Q'-L_5-$ and R_3 and R_{3a} taken together form O or S, then Cy_1 is thiophen-isoxazol, thiophen-pyrazol, thiophen-oxadiazol, thiophen-thiadiazol, thiophen-triazol, thiophen-pyridin or phenyl-triazol and Cy_2 is amino-quinazolin or pyrrolo-pyridin;

or when L_1 is O, NR_5, -S(O)p-, $-S(O)pNR_5-$, -C(X)Y- or $-L_3-Q-L_4-Q'-L_5-$ then R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, or heterocyclenyl group; or R_3 and R_4 together with the carbon atoms through which R_3 and R_4 are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, or heterocyclenyl group; or R_{1a} and R_{2a} are absent and R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form an aryl or heteroaryl group; or R_{3a} and R_{4a} are absent and R_3 and R_4 together with the carbon atoms through which R_3 and R_4 are linked form an aryl or heteroaryl group; or one or more of the pairs R_1 and R_{1a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_2 and R_{2a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_3 and R_{3a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_4 and R_{4a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group;.

or when L_1 is O, NR_5, -S(O)p-, $-S(O)pNR_5-$, -C(X)Y- or $-L_3-Q-L_4-Q'-L_5-$, then R_1, R_{1a}, R_2, R_{2a}, R_3, R_{3a}, R_4 and R_{4a} are independently $Y_1Y_2NC(O)-$ and Y_1 and Y_2 are independently hydrogen, optionally substituted alkoxy or optionally substituted aryloxy, but Y_1 and Y_2 are not simultaneously hydrogen,

or when L_1 is O, NR_5, -S(O)p-, $-S(O)pNR_5-$, -C(X)Y- or $-L_3-Q-L_4-Q'-L_5-$, then Z is –C(O)-.

2. A compound according to claim 1 wherein Cy_2 is optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted fused heteroarylheterocyclyl, optionally substituted fused heteroarylheterocyclenyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylcycloalkyl, fused arylheteroclyl, optionally substituted fused arylheterocyclenyl, or optionally substituted aryl.

3. A compound according to claim 1 wherein L_1 is absent, optionally substituted alkylene, optionally substituted alkenylene, -C(O)NR_5-, -S(O)p-, -C(O)-, -C(O)Y-C(X)Y-, -C(O)O-, C(O)NR_5-S(O)p-, -C(O)-C(O)NR_5S(O)p-, -S(O)pNR_5-, -C(O)-alkylene-O-, -C(O)-alkenylene-O-, -S(O)p-alkenylene-, -S(O)p-alkylene-, -C(O)-alkylene-C(O)-, -C(O)-alkylene-S(O)p-, -S(O)p-alkylene-C(O)-, -C(O)-alkylene, -C(O)-alkenylene-, - alkylene-C(O)NR_5-, methylene, -S(O)p-alkenylene-,-C(O)C(O)NR_5 or -C(O)CH(OH)-alkylene-.

4. A compound according to claim 1 wherein Cy_1 is optionally substituted aryl, heteroaryl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted cycloalkyl, optionally substituted cycolalkenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcycloalkyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylheterocyclyl or optionally substituted fused heteroarylheterocyclenyl.

5. A compound according to claim 1 wherein R_4 is alkoxyalkyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, alkoxycarbonylalkyl, hydroxyalkyl, acylalkyl, acylaminoalkyl or carbamoylalkyl; and R_{4a} is hydrogen and. wherein R_2 alkoxyalkyl, alkoxycarbonylalkyl, carboxyalkyl, hydroxyalkyl or heterocyclylalkyloxycarbonyl, and R_{2a} is hydrogen.

6. A compound according to claim 1 wherein

A is N;

G_1 is L_1-Cy_1 and G_2 is L_2-Cy_2;

L_1 and L_2 are independently absent, methylene, ethylene, sulfonyl, alkylenesulfonyl or alkylene;

Cy_1 is thiaheteroaryl, thiaheterocyclyl, thiaheterocyclenyl, fused thiaheteroarylcycloalkyl, fused thiaheteroarylcycloalkenyl, fused heteroarylthiacycloalkyl or fused heteroarylthiacycloalkenyl, thiophen-isoxazolyl, thieno-pyridineyl, benzo-thiophen, indolyl, morholinyl, aminopyridine-

benzyl, pyrimidin-benzyl, aminoquinazolin, pyrimidin-piperidin, thiophen-pyrazol, thiophen-oxadiazol, thiophen-thiadiazol, thiophen-triazol, thiophen-pyridin, phenyl-triazol optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcycloalkyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylheterocyclyl or optionally substituted fused heteroarylheterocyclenyl;

Cy_2 is amino-quinazolin, benzhydrylidene-amino, pyrrolo-pyridin, bipyridinyl, pyridin-benzyl, thiophenyl, thiophen-benzyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcycloalkyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylheterocyclyl, optionally substituted fused heteroarylheterocyclenyl, azaheteroaryl, azaheterocyclyl, azaheterocyclenyl, fused azaheteroarylcycloalkyl, fused azaheteroarylcycloalkenyl, fused heteroarylazacycloalkyl or fused heteroarylazacycloalkenyl;

R_3 and R_{3a} taken together form O or S;

R_2 and R_{2a} are independently selected from hydrogen, alkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, alkoxyaminoalkyl, cycloalklalkylamino, benzyloxyalkyl, isopropyl, aminomethyl, methoxyethylaminomethyl, piperazin, pyrrolidin, ethoxymethyl, benzyloxymethyl, methoxymethyl, isobutyl, isopropylamino or isopropylaminomethyl, provided that R_2 and R_{2a} are not each hydrogen, or carboxy, alkoxycarbonyl, $Y_1Y_2NC(O)$-, wherein Y_1 and Y_2 are defined as in claim 1, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl; or R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, or heterocyclenyl group; or R_{1a} and R_{2a} are absent and R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form an aryl or heteroaryl group; or R_2 and R_{2a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group;

R_1 and R_{1a} are independently selected from hydrogen, carboxy, alkoxycarbonyl, $Y_1Y_2NC(O)$-, wherein Y_1 and Y_2 are defined as in claim 1, optionally substituted alkyl, optionally substituted

aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl;

or R_1 and R_{1a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group;

R_4 and R_{4a} are independently selected from hydrogen, carboxy, alkoxycarbonyl, $Y_1Y_2NC(O)$-, wherein Y_1 and Y_2 are defined as in claim 1, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl or R_4 and R_{4a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group, or R_4 and R_{4a} taken together form O or S;

and m and n are each 1.

7. A compound according to claim 6 wherein

A is N;

G_1 is L_1-Cy_1 and G_2 is L_2-Cy_2;

L_1 is sulfonyl or alkylenesulfonyl;

L_2 is absent, methylene, ethylene or alkylene;

Cy_1 is thiaheteroaryl, thiaheterocyclyl, thiaheterocyclenyl, fused thiaheteroarylcycloalkyl, fused thiaheteroarylcycloalkenyl, fused heteroarylthiacycloalkyl or fused heteroarylthiacycloalkenyl, thiophen-isoxazolyl, thieno-pyridineyl, benzo-thiophen, indolyl, morholinyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcycloalkyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylheterocyclyl or optionally substituted fused heteroarylheterocyclenyl;

Cy_2 is amino-quinazolin, benzhydrylidene-amino, pyrrolo-pyridin, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcycloalkyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylheterocyclyl, optionally substituted fused heteroarylheterocyclenyl, azaheteroaryl, azaheterocyclyl, azaheterocyclenyl, fused

azaheteroarylcycloalkyl, fused azaheteroarylcycloalkenyl, fused heteroarylazacycloalkyl or fused heteroarylazacycloalkenyl;

R_3 and R_{3a} taken together form O or S;

R_2 and R_{2a} are independently selected from hydrogen, alkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, alkoxyaminoalkyl, cycloalklalkylamino, benzyloxyalkyl, isopropyl, aminomethyl, methoxyethylaminomethyl, piperazin, pyrrolidin, ethoxymethyl, benzyloxymethyl, methoxymethyl, isobutyl, isopropylamino or isopropylaminomethyl, provided that R_2 and R_{2a} are not each hydrogen;

R_1, R_{1a}, R_4 and R_{4a} are independently selected from hydrogen, carboxy, alkoxycarbonyl, $Y_1Y_2NC(O)$-, wherein Y_1 and Y_2 are defined as in claim 1, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl;

or the pairs R_1 and R_{1a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_4 and R_{4a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group;

and m and n are each 1.

8. A compound according to claim 6 wherein

A is N;

G_1 is L_1-Cy_1 and G_2 is L_2-Cy_2;

L_1 and L_2 are independently absent, methylene, ethylene or alkylene;

Cy_1 is thiophen-isoxazolyl, aminopyridine-benzyl, benzo-thiophen, pyrimidin-benzyl, aminoquinazolin, pyrimidin-piperidin, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcycloalkyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylheterocyclyl or optionally substituted fused heteroarylheterocyclenyl;

Cy_2 is bipyridinyl, amino-quinazolin, pyridin-benzyl, thiophenyl, thiophen-benzyl, pyrrolo-pyridin, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused

arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcycloalkyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylheterocyclyl or optionally substituted fused heteroarylheterocyclenyl;

R_3 and R_{3a} taken together form O or S; and

R_4 and R_{4a} taken together form O or S;

R_1, R_{1a}, R_2, R_{2a}, are independently selected from hydrogen, carboxy, alkoxycarbonyl, $Y_1Y_2NC(O)$-, wherein Y_1 and Y_2 are defined as in claim 1, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl; or R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, or heterocyclenyl group; or R_{1a} and R_{2a} are absent and R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form an aryl or heteroaryl group; or one or more of the pairs R_1 and R_{1a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_2 and R_{2a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group;

and m and n are each 1.

9. A compound according to claim 6 wherein

A is N;

G_1 is L_1-Cy_1 and G_2 is L_2-Cy_2;

L_1 and L_2 are independently absent, methylene, ethylene or alkylene;

Cy_1 is thiophen-isoxazol, thiophen-pyrazol, thiophen-oxadiazol, thiophen-thiadiazol, thiophen-triazol, thiophen-pyridin or phenyl-triazol;

Cy_2 is amino-quinazolin or pyrrolo-pyridin;

R_3 and R_{3a} taken together form O or S;

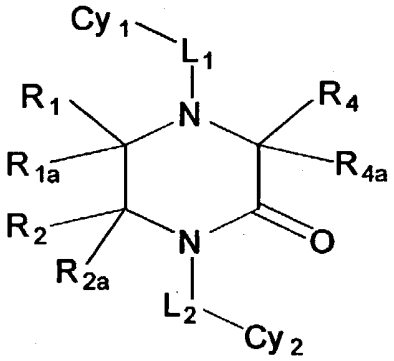
R_1, R_{1a}, R_2, R_{2a}, R_4 and R_{4a} are independently selected from hydrogen, carboxy, alkoxycarbonyl, $Y_1Y_2NC(O)$-, wherein Y_1 and Y_2 are defined as in claim 1, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl; or R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, or heterocyclenyl group; or R_{1a} and R_{2a} are absent and R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form an aryl or heteroaryl group; or one or more of the pairs R_1 and R_{1a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_2 and R_{2a} taken together with the carbon atom through

which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_4 and R_{4a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; and m and n are each 1.

10. A compound according to claims 1, 6, 7, 8 and 9 wherein Cy_2 is optionally substituted with one or more groups selected from amino, carbamoyl, acylamino, heteroaryl, heterocyclenyl, heterocyclyl, alkyl, amidino, alkyloxycarbonyl, hydroxy, alkoxy, aryl, isourea, guanidino, acylhydrazino, acyl, cyano, carboxy, sulfamoyl, or halo.

11. A compound according to claims 1, 6, 7, 8 and 9 wherein Cy_1 is optionally substituted with one or more groups selected from amino, halo, hydroxyl, aryl, heteroaryl, amidino, alkyl, acylamino, carbamoyl, cyano, alkoxy, nitro, carbamate, sulfamyl.

12. A compound according to claim 1 having the formula II

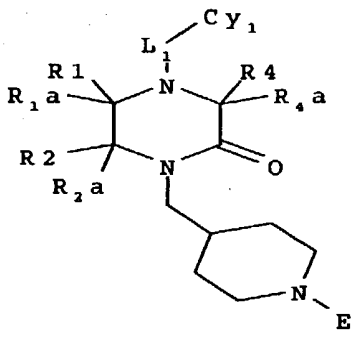


II

or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof,
wherein R_1, R_{1a}, R_2, R_{2a}, R_4, R_{4a}, Cy_1, Cy_2, L_1, and L_2 are as defined in formula I.

13. A compound according to claim 12 wherein Cy_2 contains at least one nitrogen atom and when Cy_2 is optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted fused phenylcycloalkyl or optionally substituted fused phenylcycloalkenyl, then said nitrogen atom is a basic nitrogen atom.

14. A compound according to claim 1 having the formula IIa



IIa

or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof,

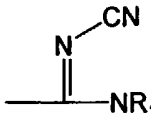
wherein

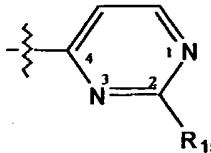
R_1, R_{1a}, R_2, R_{2a}, R_4 and R_{4a} are independently selected from hydrogen, alkyl, alkoxyalkyl, aminoalkyl, aminoalkylalkoxy, carboxy, alkoxycarbonyl, $Y_1Y_2NC(O)$-, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl, or R_1 and R_{1a}, R_2 and R_{2a} or R_4 and R_{4a} taken together form O or S; or R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, or heterocyclenyl group; or R_{1a} and R_{2a} are absent and R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form an aryl or heteroaryl group; or one or more of the pairs R_1 and R_{1a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_2 and R_{2a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_4 and R_{4a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group;

Cy_1 are independently selected from isoxazolyl, thiophenyl, thiophenyl-isoxazolyl, obtionally substituted by halogen, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcycloalkyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylheterocyclyl and optionally substituted fused heteroarylheterocyclenyl;

L_1 is absent, methylene, O, NR_5, -S(O)p-, -S(O)pNR_5-, -C(X)Y- or -L_3-Q-L_4-Q'-L_5-, -C(O)Y-C(X)Y-,

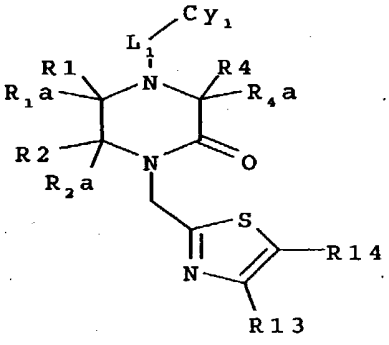
-C(X)YC(O)-, -C(C)NR_5-S(O)p-, or -C(O)C(O)NR_5S(O)p-; p is 1 or 2, and

E is alkoxycarbonyl, carbamoyl, acyl, alkyl, pyridinyl, amidino;  wherein R_{12} and $R_{12'}$ are independently selected from hydrogen or optionally substituted lower alkyl; or



wherein R_{15} is selected from halogen, alkoxy, alkylthio and Y_1Y_2N-, wherein Y_1 and Y_2 are independently, hydrogen, alkyl and aralkyl.

15. A compound according to claim 1 having the formula IIb



IIb

or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof, wherein

R_1, R_{1a}, R_2, R_{2a}, R_4 and R_{4a} are independently selected from hydrogen, carboxy, alkoxycarbonyl, $Y_1Y_2NC(O)$-, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl, or R_1 and R_{1a}, R_2 and R_{2a} or R_4 and R_{4a} taken together form O or S; or R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, or heterocyclenyl group; or R_{1a} and R_{2a} are absent and R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form an aryl or heteroaryl group; or one or more of the pairs R_1 and R_{1a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_2 and R_{2a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_4 and R_{4a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group;

Cy_1 are independently selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted fused

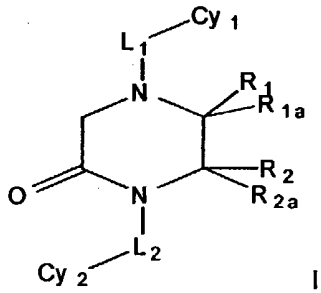
arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcycloalkyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylheterocyclyl and optionally substituted fused heteroarylheterocyclenyl;

L_1 is absent, O, NR_5, -S(O)p-, -S(O)pNR_5-, -C(X)Y- or -L_3-Q-L_4-Q'-L_5-, -C(O)Y-C(X)Y-, -C(X)YC(O)-,

-C(C)NR_5-S(O)p-, or -C(O)C(O)NR_5S(O)p-; and

R_{13} and R_{14} are independently hydrogen, lower alkyl, aryl, heteroaryl, amino, acylaminoalkyl, alkoxycarbonylalkyl, carbamoylalkyl or alkoxyalkyl; or R_{13} and R_{14} together with the carbon atoms through which R_{13} and R_{14} are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, heterocyclenyl group, aryl group or heteroaryl group.

16. A compound according to claim 1 having the formula IIc



IIc

or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof, wherein:

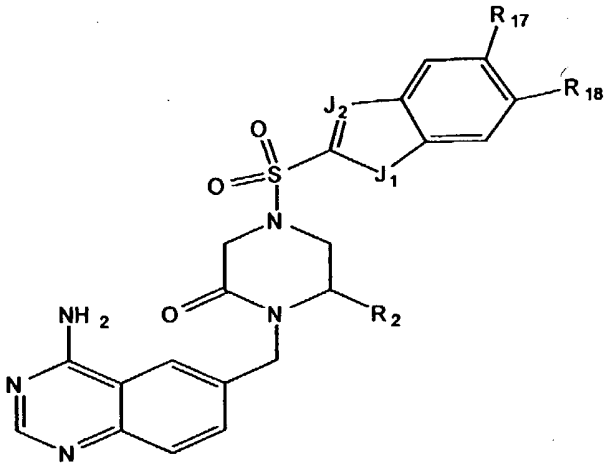
Cy_1 is thiaheteroaryl, benzothiopheneyl or azaheteroaryl, which are unsubstituted or substituted by halogen,

L_1 is -$S(O)_2$-, -$S(O)_2$-alkylene-, -$S(O)_2$-alkyenlene- or -$S(O)_2$-alkynylene-;

R_1, R_{1a}, R_2, R_{2a} are independently hydrogen, alkyl, alkoxyalkyl, aminoalkyl, aminoalkylalkoxy, carboxyl, alkoxycarbonyl, or carbamoyl; L_2 is methylene; and

Cy_2 is azaheteroaryl, azaheterocyclyl, azaheterocyclenyl, fused azaheteroarylcycloalkyl, fused azaheteroarylcycloalkenyl, fused heteroarylazacycloalkyl or fused heteroarylazacycloalkenyl.

17. A compound according to claim 1 having the formula IId



IId

wherein R_{17} and R_{18} are independently hydrogen or halogen;

J_1 is S or NH;

J_2 is CH or N; and

R_2 is hydrogen, alkyl, carboxyl, alkoxycarbonyl, or carbamoyl.

18. A compound according to claim 12 wherein L_1 and L_2 independently are methylene, ethylene, propylene or butenylene; R_1, R_{1a}, R_2, R_{2a} are independently hydrogen, alkyl, alkoxyalkyl, aminoalkyl, aminoalkylalkoxy, carboxyl, alkoxycarbonyl, or carbamoyl; Cy_1 is heteroaryl, thiaheteroaryl, biheteroaryl, thiophenyl, isoxazolyl, isoxazolyl-thiophenyl or azaheteroaryl, which are unsubstituted or substituted by halogen; Cy_2 is azaheteroaryl, quinazolin, amino-quinazolin or 4-aminoquinazolin.

19. A compound according to claim 1 selected from the group consisting of

5-Chloro-2-chlorosulfonyl-indole-1-carboxylic acid tert-butyl ester,

6-Chloro-2-chlorosulfonyl-indole-1-carboxylic acid tert-butyl ester,

3-(5-Chloro-thiophen-2-yl)-3-oxo-propionic acid tert-butyl ester,

Methyl-6-Chloro-benzofurancarboxylate,

2-Cyclopentyl-3-oxo-piperazine-1-carboxylic acid benzyl ester,

(+/-)-cis-4-benzyloxycarbonyl-decahydroquinoxalin-2-one,

5-Methyl-3-oxo-2-propyl-piperazine-1-carboxylic acid tert-butyl ester,

4-[4-Amino-quinazolin-7-ylmethyl]-5-methyl-3-oxo-2-propyl-piperazine,

(*R*)-3-Methoxymethyl-5-oxo-piperazine-1-carboxylic acid allyl ester,

6-Isopropyl-piperazin-2-one,

9-(4-Aminoquinazolin-7-ylmethyl)-6,9-diaza-spiro[4,5]decan-10-one,

(+/-)-cis-4-benzyloxycarbonyl-decahydroquinoxalin-2-one,

(+/-)-cis-1-(4-Amino-quinazolin-7-ylmethyl)-decahydroquinoxalin-2-one,,
(+/-)-trans-4-benzyloxycarbonyl-decahydroquinoxalin-2-one,
(+/-)-trans-1-(4-Amino-quinazolin-7-ylmethyl)-decahydroquinoxalin-2-one,
4-Benzyloxycarbonyl-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isopropyl-piperazin-2-one,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isopropyl-piperazin-2-one,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isopropyl-piperazin-2-one,
(R/S)1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid ethyl ester,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isopropyl-piperazin-2-one,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isopropyl-piperazin-2-one,
(4aRS,8aSR)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-octahydro-quinoxalin-2-one,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-piperazin-2-one
1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-piperazin-2-one,
[1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-(S)-yl]-acetic acid,
[1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-(S)-yl]-acetic acid tert-butyl ester,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one,
(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid (2-pyrrolidin-1-yl-ethyl)-amide,
(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid 2-pyrrolidin-1-yl-ethyl ester,

(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-piperazin-2-one,
(s)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-piperazin-2-one,
4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-sulfonic acid (4-chloro-phenyl)-amide,
1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid 2-imidazol-1-yl-ethyl ester,
(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid 2-morpholin-4-yl-ethyl ester,
(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid pyrrolidin-2-ylmethyl ester,
(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid 2-methylamino-ethyl ester,
(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methyl-piperazin-2-one,
(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methyl-piperazin-2-one,
(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isopropyl-piperazin-2-one,
(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isobutyl-piperazin-2-one,
(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isobutyl-piperazin-2-one,
(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-methyl-piperazin-2-one,
(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-methyl-piperazin-2-one,
(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one,
(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one,
(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-methyl-piperazin-2-one,

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-methyl-piperazin-2-one,

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one,

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one,

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-methyl-piperazin-2-one,

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-methyl-piperazin-2-one,

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isobutyl-piperazin-2-one,

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isobutyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(2-chloro-imidazo[1,2-a]pyridin-7-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-3(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-(S)-6-methyl-(S)-3-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-thieno[2,3-b]pyridin-2-ylmethyl)-(S)-3-propyl-piperazin-2-one,

2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo(S)--2-propyl-piperazin-1-ylmethyl]-5-chloro-indole-1-carboxylic acid tert-butyl ester,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-(S)-3-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzofuran-2-ylmethyl)-3(S)-propyl-piperazin-2-one,

9-(4-Amino-quinazolin-7-ylmethyl)-6-[3-(5-chloro-thiophen-2-yl)-allyl]-6,9-diaza-spiro[4.5]decan-10-one,

(4aRS,8aSR)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-octahydro-quinoxalin-2-one,

(4aRS,8aSR)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-octahydro-quinoxalin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-3(S)-isobutyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3(S)-isobutyl-piperazin-2-one,

3-[4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazin-1-ylmethyl]-benzamidine,

(4aRS,8aRS)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-octahydro-quinoxalin-2-one,

(4aRS,8aRS)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-octahydro-quinoxalin-2-one,

(4aRS,8aRS)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-octahydro-quinoxalin-2-one,

2-[4-(4-Amino-quinazolin-7-ylmethyl)-1-(7-chloro-isoquinolin-3-ylmethyl)-3-oxo-piperazin-2-(S)-yl]-N-methyl-acetamide,

2-[4-(4-Amino-quinazolin-7-ylmethyl)-1-(7-chloro-isoquinolin-3-ylmethyl)-3-oxo-piperazin-2-(S)-yl]-acetamide,

2-{4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(5-chloro-thiophen-2-yl)-allyl]-3-oxo-piperazin-2-(S)-yl}-acetamide,

2-{4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(5-chloro-thiophen-2-yl)-allyl]-3-oxo-piperazin-2-(S)-yl}-N-methyl-acetamide,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3(S)-isobutyl-piperazin-2-one,

(s)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-3(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-methoxymethyl-4-(4-pyrimidin-4-yl-benzyl)-piperazin-2-one,

4-[4-(2-Amino-pyrimidin-4-yl)-benzyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one,

3-Amino-5-[4-(4-amino-quinazolin-7-ylmethyl)-2(S)-methoxymethyl-3-oxo-piperazin-1-ylmethyl]-thiophene-2-carbonitrile,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3(S)-(2-methoxy-ethyl)-piperazin-2-one,

3-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazin-1-yl]-3-oxo-propenyl}-benzonitrile,

3-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazin-1-yl]-3-oxo-propenyl}-benzamidine,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-hydroxy-phenyl)-acryloyl]-(3S)-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-acryloyl]-(3S)-propyl-piperazin-2-one,

1-[4-(4-Aminoquinazoline-7-ylmethyl)-3-oxo-2-propyl-piperazine-1-yl]-3-(5-chloro-thiophen-2-yl)-propane-1,3,dione,

1-[4-(4-Aminoquinazoline-7-ylmethyl)-3-oxo-2-propyl-piperazine-1-yl]-3-(5-chloro-thiophen-2-yl)-2-fluoro-propane-1,3,dione,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl-3-(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl-3-(S)-(2-methanesulfinyl-ethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl-3-(S)-(2-methanesulfonyl-ethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-dimethylaminomethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzo-[b]thiophene-2-carbonyl)-(3S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-2-methyl-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzofuran-2-carbonyl)-(S)-6-methyl-(S)-3-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzofuran-2-carbonyl)-3(S)-(2-methylsulfanyl-ethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chlorobenzo[b]-thiophene-2-carbonyl)-(S)-3-propyl-piperazin-2-one

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzo[b]-thiophene-2-carbonyl)-(S)-6-methyl-(S)-3-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]-thiophene-2-carbonyl)-(S)-6-methyl-(S)-3-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-(S)-6-methyl-(S)-3-propyl-piperazin-2-one ,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-(S)-6-methyl-(S)-3-propyl-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-(S)-6-methyl-(S)-3-propyl-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-(S)-6-methyl-(S)-3-propyl-piperazin-2-on,
1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzofuran-2-carbonyl)-3(S)-propyl-piperazin-2-one,
3-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazin-1-yl]-2-oxo-ethyl}-benzamidine,
3-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-2-oxo-ethyl}-benzamidin,
4-[3-(4-Amino-cyclohexyl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-(3S)-propyl-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-(S)-3-propyl-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzofuran-2-carbonyl)-3(S)-propyl-piperazin-2-one trifluoroacetate,
1-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-2-propyl-piperazin-1-yl]-3-(3-chloro-phenyl)-propane-1,3-dione,
4-[(5-Amino-pyridin-2-yloxy)-acetyl]-1-(4-amino-quinazolin-7-ylmethyl)-(S)-3-methoxymethyl-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(R)-methoxymethyl-piperazin-2-one,
3-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-3-oxo-propyl}-benzamidine,
3-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazin-1-yl]-3-oxo-propyl}-benzamidine,
1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-imidazol-1-yl-benzoyl)-3(S)-propyl-piperazin-2-one,
(6-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-methoxymethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-pyridin-3-yl)-carbamic acid tert-butyl ester,
(4aRS,8aSR)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-octahydro-quinoxalin-2-one,
(4aRS,8aRS)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-octahydro-quinoxalin-2-one,
(4aRS,8aRS)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-octahydro-quinoxalin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-6-oxo-1,6-dihydro-pyridin-3-yl)-acryloyl]-(S)-3-propyl-piperazin-2-one ,

1-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-2-propyl-piperazin-1-yl]-3-(4-hydroxy-phenyl)-propane-1,3-dione,

2-{4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-oxo-piperazin-2-(S)-yl}-acetamide,

2-{4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-oxo-piperazin-2-(S)-yl}-acetamide,

2-{4-(4-Amino-quinazolin-7-ylmethyl)-1-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-oxo-piperazin-2-(S)-yl}-acetamide,

{4-(4-Amino-quinazolin-7-ylmethyl)-1-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-oxo-piperazin-2-(S)-yl}-acetic acid methyl ester

2-{4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-oxo-piperazin-2-(S)-yl}-N-methyl-acetamide,

2-{4-(4-Amino-quinazolin-7-ylmethyl)-1-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-oxo-piperazin-2-(S)-yl}-N-methyl-acetamide,

2-{4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-oxo-piperazin-2-(S)-yl}-N-methyl-acetamide,

4-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-methoxymethyl-3-oxo-piperazin-1-yl]-3-oxo-propenyl}-benzenesulfonamide,

N-(5-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazin-1-yl]-3-oxo-propyl}-pyridin-2-yl)-acetamide,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-amino-[1,3,4]thiadiazol-2-ylsulfanyl)-acetyl]-(S)-3-propyl-piperazin-2-one

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-amino-[1,3,4]thiadiazol-2-ylsulfanyl)-acetyl]-(S)-3-methoxymethyl-piperazin-2-one,

3-[4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carbonyl]-benzamidine,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(piperidin-3-yloxy)-acetyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-4-hydroxy-phenyl)-(E)-acryloyl]-(3S)-methoxymethyl-piperazin-2-one,

(3S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-hydroxy-naphthalene-2-carbonyl)-3-propyl-piperazin-2-one,

(3S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-hydroxy-1H-indole-2-carbonyl)-3-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-hydroxy-phenoxy)-acetyl]-(3S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-hydroxy-phenyl)-acryloyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one,

N-(5-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-2-(S)-propyl-piperazin-1-yl]-3-oxo-propenyl}-pyridin-2-yl)-acetamide,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-phenoxy)-acetyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3,6-bis-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-acryloyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one,

4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-(R)-6-methyl-(S)-3-propyl-piperazin-2-one,

2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-(S)-2-propyl-piperazin-1-yl]-N-(5-chloro-thiophen-2-yl)-2-oxo-acetamide,

2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-N-(5-chloro-thiophen-2-yl)-2-oxo-acetamide,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-3-yl)-acryloyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one,

2-[4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-methoxymethyl-3-oxo-piperazin-1-yl]-N-(5-chloro-thiophen-2-yl)-2-oxo-acetamide,

(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3,4-dihydroxy-phenyl)-(E)-acryloyl]-(3S)-methoxymethyl-piperazin-2-one,

4-[3-(6-Amino-pyridin-3-yl)-propionyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one,

4-[3-(6-Amino-pyridin-3-yl)-propionyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-(S)-hydroxymethyl-piperazin-2-one,

N-(5-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-butyl-3-oxo-piperazin-1-yl]-3-oxo-propenyl}-6-methyl-pyridin-2-yl)-acetamide,

N-(5-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-butyl-3-oxo-piperazin-1-yl]-3-oxo-propenyl}-pyridin-2-yl)-acetamide,

4-[3-(6-Amino-2-methyl-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-butyl-piperazin-2-one

1-[4-(4-Aminoquinazoline-7-ylmethyl)-3-oxo-piperazin-1-yl]-3-(5-chloro-thiophen-2-yl)-propane-1,3,dione,

4-[3-(3-Amino-4-chloro-phenyl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-(3S)-methoxymethyl-piperazin-2-one,

4-[3-(3-Amino-5-chloro-phenyl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-(3S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-thiophen-2-yloxy)-acetyl]-(R)-6-methyl-(S)-3-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-benzenesulfinyl)-acetyl]-(3-S)-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-hydroxy-phenoxy)-acetyl]-(3S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-phenylsulfanyl)-acetyl]-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-benzenesulfinyl)-acetyl]-(3S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-hydroxy-phenyl)-(E)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-hydroxy-phenyl)-(E)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-hydroxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-hydroxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3,6-bis-methoxymethyl-piperazin-2-one,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-methoxymethyl-piperazin-2-one,
4-[(6-Amino-pyrimidin-4-yloxy)-acetyl]-1-(4-amino-quinazolin-7-ylmethyl)-3(S)-methoxymethyl-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-benzenesulfonyl)-acetyl]-piperazin-2-one,
1-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-3-(4-chloro-phenyl)-propane-1,3-dione
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-phenylsulfanyl)-acetyl]-piperazin-2-one,
4-[3-(6-Amino-2-methyl-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-propyl-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-3-hydroxy-acryloyl]-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-dimethylamino-phenyl)-acryloyl]-(3S)-propyl-piperazin-2-one,
3-(S)-6-(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-hydroxymethyl-3-methoxymethyl-piperazin-2-one,
4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3(S)-isobutyl-piperazin-2-one,
4-[3-(2-Amino-pyrimidin-5-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3(S)-propyl-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-hydroxy-phenyl)-acryloyl]-(3S)-propyl-piperazin-2-one,
4-[3-(3-Amino-phenyl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-(3S)-methoxymethyl-piperazin-2-one,
4-[3-(4-Amino-3-chloro-phenyl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-(3S)-methoxymethyl-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-pyrazin-2-yloxy)-acetyl]-(S)-3-methoxymethyl-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-pyrazin-2-yloxy)-acetyl]-(S)-3-propyl-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3(S)-isobutyl-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3(S)-isobutyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2-amino-thiazol-4-yl)-acetyl]-(S)-3-propyl-piperazin-2-one,

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-6-oxo-piperazine-2-carboxylic acid ethyl ester,

4-[3-(4-Amino-phenyl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-(3S)-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3,4-dichloro-thiophen-2-yloxy)-acetyl]-(S)-3-propyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3,4-dichloro-thiophen-2-yloxy)-acetyl]-(S)-3-methoxymethyl-piperazin-2-one,

4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3(S)-(2-methoxy-ethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3(S)-(2-methoxy-ethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3(S)-(2-methoxy-ethyl)-piperazin-2-one,

4-(4-Amino-quinazolin-7-ylmethyl)-(S)-5-methyl-3-oxo-(S)-2-propyl-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-(S)-5-methyl-3-oxo-(S)-2-propyl-piperazine-1-carboxylic acid (5-chloro-thiophen-2-yl)amide,

4-(4-Amino-quinazolin-7-ylmethyl)-2(S)-isobutyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-hydroxymethyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,

(2S)-4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-2-propyl-piperazine-1-carboxylic acid (5-bromo-thiazol-2-yl)-amide,

(2S)-4-(4-Amino-quinazolin-7-ylmethyl)-2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-chloro-thiazol-2-yl)-amide,

(2S)-4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-2-propyl-piperazine-1-carboxylic acid (5-chloro-thiazol-2-yl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-hydroxy-phenyl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methylcarbamoylmethyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,

4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-carbamoylmethyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,

(4aRS,8aRS)-4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-octahydro-quinoxaline-1-carboxylic acid (4-chloro-phenyl)-amide,
4-(4-Amino-quinazolin-7-ylmethyl)-2(S)-(2-methylsulfanyl-ethyl)-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,
4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-chloro-furan-2-yl)-amide,
(2S)-4-(4-Amino-quinazolin-7-ylmethyl)-2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-bromo-thiazol-2-yl)-amide,
N-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-(S)-2-propyl-piperazine-1-carbonyl]-4-chloro-benzenesulfonamide,
1-(S)-4-(4-Amino-quinolin-7-ylmethyl)-3-oxo-2-propyl-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,
1-(S)-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-propyl-piperazin-2-one,
1-(S)-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-4-oxy-3-propyl-piperazin-2-one,
1-(S)-4-(4-Amino-quinolin-7-ylmethyl)-2-methoxymethyl-3-oxo-2-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,
(S)-4-(4-Aminoquinolin-7-ylmethyl)-2-methoxylmethyl-3-oxo-2-piperazine-1-carboxylic acid (5-chlorothiophen-2-yl)-amide,
1-(S)-4-(4-Amino-quinolin-7-ylmethyl)-2-methyl-3-oxo-2-piperazine-1-carboxylic acid phenylamide,
1-(S)-4-(4-Amino-quinolin-7-ylmethyl)-2-methyl-3-oxo-2-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,
1-(S)-4-(4-Amino-cinnolin-7-ylmethyl)-2-methyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide,
1-(S)-(4-Amino-cinnolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-methyl-piperazin-2-one,
1-(4-Amino-cinnolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-methyl-piperazin-2-one,
4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(+)-carboxylic acid methyl ester,
4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(-)-carboxylic acid methyl ester,
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(+)-carboxylic acid amide,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-
(-)-carboxylic acid amide,
4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-hydroxymethyl-1-(1-methyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-hydroxymethyl-1-(1-methyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-(5-Chloro-1H-indole-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-(5-Chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-(7-Methoxy-naphthalene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-(Benzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-[4-(5-Chloro-thiophen-2-yl)-benzyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-[3-(5-Chloro-thiophen-2-yl)-benzyl]-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-[3-(5-Chloro-thiophen-2-yl)-benzyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-[5-(5-Chloro-thiophen-2-yl)-pyridin-2-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-[5-(5-Chloro-thiophen-2-yl)-pyridin-2-ylmethyl]-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-[5-(5-Chloro-thiophen-2-yl)-pyridin-2-ylmethyl]-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-[2-(4-Chloro-phenyl)-1H-indol-3-ylmethyl]-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-[6-(5-Chloro-thiophen-2-yl)-pyridin-2-ylmethyl]-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-[4-(5-Chloro-thiophen-2-yl)-benzyl]-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-[6-(5-Chloro-thiophen-2-yl)-pyridin-2-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(5-Chloro-[2,3']bithiophenyl-5'-ylmethyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(5'-Chloro-[2,2']bithiophenyl-5-ylmethyl)-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[2,2']Bithiophenyl-5-ylmethyl-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(5-Chloro-[2,3']bithiophenyl-5'-ylmethyl)-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[6-(5-Chloro-thiophen-2-yl)-pyridin-2-ylmethyl]-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[3-(5-Chloro-thiophen-2-yl)-4-fluoro-benzyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[5-(3-Chloro-phenyl)-furan-2-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[4-(5-Chloro-thiophen-2-yl)-benzyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[3-(5-Chloro-thiophen-2-yl)-4-fluoro-benzyl]-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[4-(5-Chloro-thiophen-2-yl)-benzyl]-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[5-(3-Chloro-phenyl)-furan-2-ylmethyl]-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[3-(5-Chloro-thiophen-2-yl)-allyl]-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(5-Chloro-1H-indol-2-ylmethyl)-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-(5'-Chloro-[2,2']bithiophenyl-5-ylmethyl)-3-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[4-(5-Chloro-thiophen-2-yl)-benzyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[5-(5-Chloro-thiophen-2-yl)-pyridin-2-ylmethyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-2-methyl-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-propyl-piperazin-2-one,

7-{4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-2-oxo-(S)-3-propyl-piperazin-1-ylmethyl}-3H-quinazolin-4-one,

7-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-2-oxo-(S)-3-propyl-piperazin-1-ylmethyl}-3H-quinazolin-4-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-(S)-6-methyl-(S)-3-propyl-piperazin-2-one

4-[3-(5-Chloro-thiophen-2-yl)-allyl]-(S)-3-ethyl-1-(4-hydroxy-quinolin-7-ylmethyl)-piperazin-2-one,

7-{4-[3-(5-Chloro-thiophen-2-yl)-allyl]-3-(S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-2H-isoquinolin-1-one,

7-[4-(7-Chloro-isoquinolin-3-ylmethyl)-3-(S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl]-2H-isoquinolin-1-one,

4-(5-Chloro-1H-indol-2-ylmethyl)-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one,

4-(5-Chloro-1H-indol-2-ylmethyl)-3-(S)-methyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one,

6-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-3-methyl-3H-quinazolin-4-one,

6-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-3H-quinazolin-4-one,

4-(7-Chloro-isoquinolin-3-ylmethyl)-3-(S)-methyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one,

4-(7-Chloro-isoquinolin-3-ylmethyl)-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one,

4-(7-Chloro-isoquinolin-3-ylmethyl)-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-(S)-methyl-piperazin-2-one,

4-(7-Chloro-isoquinolin-3-ylmethyl)-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one,

4-(7-Chloro-isoquinolin-3-ylmethyl)-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-piperazin-2-one

4-(7-Chloro-isoquinolin-3-ylmethyl)-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one,

4-(7-Chloro-isoquinolin-3-ylmethyl)-3-(S)-methoxymethyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one,

4-[3-(6-Amino-pyridin-3-yl)-propionyl]-3-(S)-methoxymethyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one,

(S)-4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-6-methoxymethyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-piperazin-2-one,

4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-3(S)-isobutyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one,
4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-(3-imidazol-1-yl-benzyl)-3-(S)-methoxymethyl-piperazin-2-one,
4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3(S)-isobutyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one,
4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-3(S)-isobutyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one,
4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one,
4-[(5-Chloro-thiophen-3-yloxy)-acetyl]-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one,
4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one,
4-[3-(4-Chloro-thiophen-2-yl)-acryloyl]-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one,
4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one,
4-[3-(4-Chloro-thiophen-2-yl)-acryloyl]-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one,
4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one,
4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one,
4-[(5-Chloro-thiophen-3-yloxy)-acetyl]-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-(S)-propyl-piperazin-2-one,
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-6,7-dihydro-5H-benzothiazol-4-one,
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4-methyl-thiazole-5-carboxylic acid methylamide,
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4-methyl-thiazole-5-carboxylic acid dimethylamide,
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-pyridin-4-yl-thiazol-2-ylmethyl)-piperazin-2-one hydrobromide,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid amide,

{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-acetic acid methyl ester,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid ethyl este,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4-methyl-thiazole-5-carboxylic acid methyl ester,

1-(4-tert-Butyl-thiazol-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[4-(5-chloro-thiophen-2-yl)-thiazol-2-ylmethyl]-piperazin-2-one,

1-[4-(4-Bromo-phenyl)-thiazol-2-ylmethyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,

1-[4-(3-Bromo-phenyl)-thiazol-2-ylmethyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-methyl-thiazol-2-ylmethyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-pyridin-3-yl-thiazol-2-ylmethyl)-piperazin-2-one,

1-(5-Acetyl-4-methyl-thiazol-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,

3-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-3-methyl-butyric acid ethyl ester,

1-(4-Adamantan-1-yl-thiazol-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,

1-(4-Adamantan-1-yl-thiazol-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-phenyl-thiazol-2-ylmethyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[4-(4-hydroxy-phenyl)-thiazol-2-ylmethyl]-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[4-(4-hydroxy-phenyl)-thiazol-2-ylmethyl]-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4,5,6,7-tetrahydro-benzothiazol-2-ylmethyl)-piperazin-2-one,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid dimethylamide,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid ethyl ester,
2-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-benzoic acid,
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[4-(2-hydroxy-phenyl)-thiazol-2-ylmethyl]-piperazin-2-one,
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-pyridin-2-yl-thiazol-2-ylmethyl)-piperazin-2-one,
2-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-benzamide,
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridin-2-ylmethyl)-piperazin-2-one
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(5-methyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4,5,6,7-tetrahydro-thiazolo[4,5-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(5-methyl-4,5,6,7-tetrahydro-thiazolo[4,5-c]pyridin-2-ylmethyl)-piperazin-2-one,
2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4,7-dihydro-5H-thiazolo[4,5-c]pyridin-6-one,
(R)-2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid amide,
(R)-4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-1-(4,5,6,7-tetrahydro-benzothiazol-2-ylmethyl)-piperazin-2-one,
(R)-2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid ethyl ester,
(R)-2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-4-methyl-thiazole-5-carboxylic acid dimethylamide,
(R)-4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-1-(4-pyridin-3-yl-thiazol-2-ylmethyl)-piperazin-2-one,
(R)-3-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-3-methyl-butyric acid ethyl ester,
(R)-2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid,
(R)-2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid dimethylamide,

(S)-2-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-(3S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid amide,

(S)-2-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-(3S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-thiazole-4-carboxylic acid ethyl ester,

(S)-2-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3(S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-thiazole-4-carboxylic acid dimethylamide,

(S)-(2-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3(S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-thiazol-4-yl)-acetic acid methyl ester,

(S)-4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3(S)-methoxymethyl-1-(4,5,6,7-tetrahydro-benzothiazol-2-ylmethyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-hydroxy-4,5,6,7-tetrahydro-benzothiazol-2-ylmethyl)-piperazin-2-one,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-6,7-dihydro-5H-benzothiazol-4-one oxime,

1-(4-Amino-benzothiazol-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-5,6,7,8-tetrahydro-thiazolo[4,5-c]azepin-4-one,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid dimethylamide,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[4-(pyrrolidine-1-carbonyl)-thiazol-2-ylmethyl]-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[4-(morpholine-4-carbonyl)-thiazol-2-ylmethyl]-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[4-(piperazine-1-carbonyl)-thiazol-2-ylmethyl]-piperazin-2-one,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid N',N'-dimethyl-hydrazine,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid (2-hydroxy-ethyl)-methyl-amide,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[4-(3-hydroxy-pyrrolidine-1-carbonyl)-thiazol-2-ylmethyl]-piperazin-2-one,

2-(4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid methoxy-methyl-amide,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid isopropyl-methyl-amide,

({2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carbonyl}-methyl-amino)-acetic acid ethyl ester,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxamide,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid methylamide,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid isopropylamide,

{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-acetic acid,

2-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-acetamide,

2-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-N-methyl-acetamide,

2-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-N-isopropyl-acetamide,

2-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-N,N-dimethyl-acetamide,

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4,7-dihydro-5H-thiazolo[5,4-c]pyridin-6-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-piperidin-4-ylmethyl-piperazin-2-one,

4-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-piperidine-1-carboxylic acid amide,

2-{4-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-piperidin-1-yl}-acetamide,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[1-(2-chloro-pyrimidin-4-yl)-piperidin-4-ylmethyl]-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-piperazin-2-one,

(R)-4-(5-chloro-1H-indole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-piperazin-2-one,

(R)-4-(6-chloro-1H-indole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-piperazin-2-one,

(R)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-piperazin-2-one,
(R)-4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-methyl-piperazin-2-one,
(R)-4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-methoxymethyl-piperazin-2-one,
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-oxo-piperazine-2-carboxylic acid methyl ester,
(R)-4-(5-chloro-1H-indole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-methyl-piperazin-2-one,
(R)-4-(5-chloro-1H-indole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-methoxymethyl-piperazin-2-one,
4-(5-chloro-1H-indole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-oxo-piperazine-2-carboxylic acid methyl ester,
(R)-4-(6-chloro-1H-indole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-methyl-piperazin-2-one,
(R)-4-(6-chloro-1H-indole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-methoxymethyl-piperazin-2-one,
4-(6-chloro-1H-indole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-oxo-piperazine-2-carboxylic acid methyl ester,
(R)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-methyl-piperazin-2-one,
(R)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-methoxymethyl-piperazin-2-one,
4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-6-oxo-piperazine-2-carboxylic acid methyl ester,
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-{1-[2-(2-hydroxy-ethylamino)-pyrimidin-4-yl]-piperidin-4-ylmethyl}-piperazin-2-one,
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-{1-[2-(4-dimethylamino-butylamino)-pyrimidin-4-yl]-piperidin-4-ylmethyl}-piperazin-2-one,
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-{1-[2-(3-imidazol-1-yl-propylamino)-pyrimidin-4-yl]-piperidin-4-ylmethyl}-piperazin-2-one,
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-{1-[2-(3-morpholin-4-yl-propylamino)-pyrimidin-4-yl]-piperidin-4-ylmethyl}-piperazin-2-one,

4-[(4-{4-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-piperidin-1-yl}-pyrimidin-2-yl)-methyl-amino]-butyric acid,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-{1-[2-(2-dimethylamino-ethoxy)-pyrimidin-4-yl]-piperidin-4-ylmethyl}-piperazin-2-one,

Example 1270 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1-{2-[2-(2-oxo-imidazolidin-1-yl)-ethylamino]-pyrimidin-4-yl}-piperidin-4-ylmethyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-{1-[2-(2-dimethylamino-ethylsulfanyl)-pyrimidin-4-yl]-piperidin-4-ylmethyl}-piperazin-2-one,

4-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1-pyrimidin-2-yl-piperidin-4-ylmethyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1-pyrazin-2-yl-piperidin-4-ylmethyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-ylmethyl)-piperazin-2-one,

4-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-carboxylic acid,

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(6'-methoxy-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-ylmethyl)-piperazin-2-one,

4-(6-Chloro-benzo[b]thiophene-sulfonyl)-1-(6'-methoxy-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4-ylmethyl)-piperazin-2-one,

O-Phenyl-1-cyano-3-{4-[(chlorobenzo[b]thiophene-2-sulfonyl)-2-(keto)piperazin-1-yl]methylpiperdinyl} isourea,

Preparation of N,N Dimethyl-2-{4-[6-(chlorobenzo[b]thiophene-2-sulfonyl)-2-(keto)piperazin-1-yl]methylpiperdin-1-yl]} cyanoformamidine,

Preparation of N-Methyl-2-{4-[6-(chlorobenzo[b]thiophene-2-sulfonyl)-2-(keto)piperazin-1-yl]methylpiperdin-1-yl]} cyanoformamidine,

Preparation of N-trans-[{4-(5-Chloro-thiophen-2-yloxy)-acetyl-2-keto-3-(*S*)-methoxymethyl}-piperazin-1-yl]methylcyclohexyl-cyanoguanidine,

N-trans-[{4-(5-Chloro-thiophen-2-yloxy)-acetyl-2-keto-3-(*S*)-methoxymethyl}-piperazin-1-yl]methylcyclohexyl-N',N'-dimethyl-cyanoguanidine,

N-trans-[{4-(5-Chloro-thiophen-2-yloxy)-acetyl-2-keto-3-(*S*)-methoxymethyl}-piperazin-1-yl]methylcyclohexyl-N'-methyl-cyanoguanidine

N-trans-[{4-(5-Chloro-thiophen-2-yloxy)-acetyl-2-keto-3-(*S*)-methoxymethyl}-piperazin-1-yl]methylcyclohexyl-N'-(2-hydroxyethyl)-N'-methyl-cyanoguanidine,

Preparation of 4-[(5-Chlorothiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-cis-(4-morpholin-4-yl-cyclohexylmethyl)-piperazin-2-one,

and 4-[(5-Chlorothiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-trans-(4-morpholin-4-yl-cyclohexylmethyl)-piperazin-2-one,

4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-trans-{4-[(2-hydroxy-ethyl)-methyl-1-amino]-cyclohexylmethyl)-3-(*S*)-methoxymethyl-piperazin-2-one,

4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-cis-{4-[2-(R,S)-(1-methyl-pyrrolidin-2-yl)-ethylamino]-cyclohexylmethyl}-piperazine-2-one,

4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-trans-{4-[2-(R,S)-(1-methyl-pyrrolidin-2-yl)-ethylamino]-cyclohexylmethyl}-piperazine-2-one,

4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-cis-[4-(2-pyridin-2-yl-ethylamino)-cyclohexylmethyl]-piperazin-2-one,

4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-trans-[4-(2-pyridin-2-yl-ethylamino)-cyclohexylmethyl]-piperazin-2-one,

4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-cis-[4-(2-dimethylamino-ethylamino)-cyclohexylmethyl]-3-(S)-methoxymethyl-piperazin-2-one,

4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-trans-[4-(2-dimethylamino-ethylamino)-cyclohexylmethyl]-3-(S)-methoxymethyl-piperazin-2-one,

4-(4-cis-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-piperazine-1-carboxylic acid ethyl ester,

4-(4-trans-{4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-2-oxo-piperazin-1-ylmethyl}-piperazine-1-carboxylic acid ethyl ester,

4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-cis-([4-(4-hydroxy-piperidin-1-yl)-cyclohexylmethyl]-3-(S)-methoxymethyl-piperazin-2-one,

4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-trans-([4-(4-hydroxy-piperidin-1-yl)-cyclohexylmethyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-cis-(4-Azepan-1-yl-cyclohexylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,

1-trans-(4-Azepan-1-yl-cyclohexylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one,

4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-cis-{4-[(pyridin-2-ylmethyl)-amino]-cyclohexylmethyl}-piperazin-2-one,

4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-trans-{4-[(pyridin-2-ylmethyl)-amino]-cyclohexylmethyl}-piperazin-2-one,
4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-cis-(4-phenylamino-cyclohexylmethyl)-piperazin-2-one,
4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-1-trans-(4-phenylamino-cyclohexylmethyl)-piperazin-2-one,
4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-cis-{4-[2-(2-hydroxy-ethoxy)-ethylamino]-cyclohexylmethyl}-3-(S)-methoxymethyl-piperazin-2-one,
4-[(5-Chloro-thiophen-2-yloxy)-acetyl]-1-trans-{4-[2-(2-hydroxy-ethoxy)-ethylamino]-cyclohexylmethyl}-3-(S)-methoxymethyl-piperazin-2-one,
4-[(5-Chlorothiophen-2-yloxy)-acetyl]-1-[(2-{[N,N-dimethylaminoethyl]-amino}-pyrimidin-5-yl)-methyl]-3-(*S*)-methoxymethyl-piperazine-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-allyl]-piperazine-2,3-dione,
1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-yl-methyl)-piperazine-2,3-dione,
1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-allyl]-piperazine-2,3-dione,
1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-ylmethyl)-piperazine-2,3-dione,
1-(3-carbamimidoyl-benzyl)-4-(4-carbamimidoyl-benzyl)-2,3 dioxopiperizine,
Bis-1,4-(3-carbamimidoyl-benzyl)-2,3-dioxopiperizine,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-allyl]-piperazine-2,3-dione,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazine-2,3-dione,
1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-yl-methyl)-piperazine-2,3-dione,
1-(4-Amino-quinolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-ylmethyl)-piperazine-2,3-dione,
1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazine-2,3-dione,
1-[3-(3-chloro-phenyl)-allyl]-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2,3-dione,
1-[3-(4-chloro-phenyl)-allyl]-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2,3-dione,
1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2,3-dione,
1-(6-chloro-benzo[b]thiophen-2-yl-methyl)-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2,3-dione,
1-(5'-chloro-[2,2']bithiophenyl-5-ylmethyl)-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2,3-dione,
1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)-piperazine-2,3-dione,
1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-(thieno[3,2-b]pyridin-2-ylmethyl)-piperazine-2,3-dione,

1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-(4-pyridin-2-yl-benzyl)-piperazine-2,3-dione,
1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-[4-(1-hydroxy-pyridin-2-yl)-benzyl]-piperazine-2,3-dione,
1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-(4-pyridin-4-yl-benzyl)-piperazine-2,3-dione,
1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-[4-(1-hydroxy-pyridin-4-yl)-benzyl]-piperazine-2,3-dione,
1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-[4-(6-methoxy-pyridin-3-yl)-benzyl]-piperazine-2,3-dione,
1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazine-2,3-dione,
1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-[4-(2-dimethylamino-pyrimidin-4-yl)-benzyl]-piperazine-2,3-dione,
1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-(4-{2-[(2-dimethylamino-ethyl)-methyl-amino]-pyrimidin-4-yl}-benzyl)-piperazine-2,3-dione,
1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-[4-(2-dimethylamino-pyrimidin-4-yl)-cyclohexymethyl]-piperazine-2,3-dione,
1-[3-(5-chloro-thiophen-2-yl)-allyl]-4-(4-{2-[(2-dimethylamino-ethyl)-methyl-amino]-pyrimidin-4-yl}-cyclohexylmethyl)-piperazine-2,3-dione,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-5-methyl-piperazine-2,3-dione,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-5-ethyl-piperazine-2,3-dione,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-5-propyl-piperazine-2,3-dione,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-5-butyl-piperazine-2,3-dione,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-5-isopropyl-piperazine-2,3-dione,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-5-isobutyl-piperazine-2,3-dione,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-5-methoxymethyl-piperazine-2,3-dione,
4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(5-chloro-thiophen-2-yl)-allyl]-5,6-dioxopiperazine-2-carboxylic acid,
4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(5-chloro-thiophen-2-yl)-allyl]-5,6-dioxopiperazine-2-carboxylic acid methyl ester,
4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(5-chloro-thiophen-2-yl)-allyl]-5,6-dioxopiperazine-2-carboxylic acid amide or

4-(4-Amino-quinazolin-7-ylmethyl)-1-[3-(5-chloro-thiophen-2-yl)-allyl]-5,6-dioxopiperazine-2-carboxylic acid methyl amide
or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

20. A compound according to claim 1 selected from the group consisting of
(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-piperazin-2-one,
(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid (2-pyrrolidin-1-yl-ethyl)-amide,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one,
[1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-(S)-yl]-acetic acid,
1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-piperazin-2-one,

(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one,
2-Amino-4-[4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-2-(r)-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-benzonitrile,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isopropyl-piperazin-2-one,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isopropyl-piperazin-2-one,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one,
(R/S)1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid ethyl ester,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isopropyl-piperazin-2-one,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isopropyl-piperazin-2-one,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isopropyl-piperazin-2-one,

(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isopropyl-piperazin-2-one,

(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isopropyl-piperazin-2-one,

(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isobutyl-piperazin-2-one,

(S)-1-(4-Amino-6-chloro-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isobutyl-piperazin-2-one,

(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one,

(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one,

(6S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-methyl-piperazin-2-one,

(6S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methyl-piperazin-2-one,

(6S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-methyl-piperazin-2-one,

(6S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-methyl-piperazin-2-one,

(R/S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester,

(R/S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester,

(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one,

(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isobutyl-piperazin-2-on,e

1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-bromo-5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-3-methyl-1H-indol-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(3,5-dichloro-1H-indol-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-3-pyrrolidin-1-ylmethyl-1H-indol-2-ylmethyl)-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-3-morpholin-4-ylmethyl-1H-indol-2-ylmethyl)-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-3-methylaminomethyl-1H-indol-2-ylmethyl)-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-3-dimethylaminomethyl-1H-indol-2-ylmethyl)-piperazin-2-one,
(S)-4-[4-(6-Chloro-1H-benzoimidazole-2-sulfonyl)-2-isobutyl-6-oxo-piperazin-1-ylmethyl]-benzamidine,
(S)-4-[4-(5-Chloro-1H-indole-2-sulfonyl)-2-isobutyl-6-oxo-piperazin-1-ylmethyl]-benzamidine,
(S)-4-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-isobutyl-6-oxo-piperazin-1-ylmethyl]-benzamidine,
(S)-4-[4-(6-Chloro-1H-indole-2-sulfonyl)-2-isobutyl-6-oxo-piperazin-1-ylmethyl]-benzamidine,
1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-isobutyl-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-methoxymethyl-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-methoxymethyl-piperazin-2-one,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-isobutyl-piperazin-2-one,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-6-methoxymethyl-piperazin-2-one,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-6-isobutyl-piperazin-2-one,
(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-6-methoxymethyl-piperazin-2-one,
(6S)-2-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-isoindole-1,3-dione,
(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-6-isobutyl-piperazin-2-one,
(6S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-morpholin-4-ylmethyl-piperazin-2-one,
(6S)-6-Aminomethyl-1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-

one,

(6S)-N-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-acetamide

4-(3-Acetyl-5-chloro-1H-indol-2-ylmethyl)-1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one,

(6S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-pyrrolidin-1-ylmethyl-piperazin-2-one

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazine-2-carboxylic acid,

(2S)-N-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-methanesulfonamide,

(2S)-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-carbamic acid methyl ester,

(2S)-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-carbamic acid isopropyl ester,

(2S)-1-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-3-phenyl-urea,

(2S)-5-Bromo-thiophene-2-sulfonic acid [1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-amide,

(2S)-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-urea,

(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-(isopropylamino-methyl)-piperazin-2-one,

(2S)-1-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-3-ethyl-urea,

(2S)-N-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-formamide,

(2S)-Furan-2-carboxylic acid [1-(4-amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-ylmethyl]-amide,

(S)-[1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-oxo-piperazin-2-yl]-acetic acid,

(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-3-methyl-1H-indol-2-ylmethyl)-3-methoxymethyl-piperazin-2-one,

1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-3-fluoro-1H-indol-2-ylmethyl)-piperazin-2-one,

(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(3,5-dichloro-1H-indol-2-ylmethyl)-3-methoxymethyl-piperazin-2-one,
(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-6-(isopropylamino-methyl)-piperazin-2-one,
(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-(isopropylamino-methyl)-piperazin-2-one,
(6S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-pyrrolidin-1-ylmethyl-piperazin-2-one,
(6R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-methoxymethyl-piperazin-2-one,
(2R)-N-{1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl}-N-(2-isopropoxy-ethyl)-formamide,
(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-[(2-isopropoxy ethylamino)-methyl]-piperazin-2-one,
(6S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-piperidin-1-ylmethyl-piperazin-2-one,
(6S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-[(cyclopentyl-methyl-amino)-methyl]-piperazin-2-one,
(6R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-ethoxymethyl-piperazin-2-one or
(6R)-1-(4-Amino-quinazolin-7-ylmethyl)-6-benzyloxymethyl-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-piperazin-2-one
or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

21. A compound according to claim 1 selected from the group consisting of
(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-piperazin-2-one,
(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid 2-pyrrolidin-1-yl-ethyl ester,
[1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-(S)-yl]-acetic acid tert-butyl ester,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-(isopropylamino-methyl)-piperazin-2-one,

(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isopropyl-piperazin-2-one,
(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isobutyl-piperazin-2-one,
(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one,
(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one,
(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isobutyl-piperazin-2-one,
(R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one,
(6S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-(4-methyl-piperazin-1-ylmethyl)-piperazin-2-one,
(6S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-{[(2-dimethyl-amino-ethyl)-methyl-amino]-methyl}-piperazin-2-one,
(6S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-pyrrolidin-1-ylmethyl-piperazin-2-one,
(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-(isopropylamino-methyl)-piperazin-2-one,
(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-(isopropylamino-methyl)-piperazin-2-one,
(2R)-N-{1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-6-oxo-piperazin-2-ylmethyl}-N-(2-isopropoxy-ethyl)-formamidine,
(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-[([1,3]dioxolan-2-ylmethyl-methyl-amino)-methyl]-piperazin-2-one,
(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-(4-pyrrolidin-1-yl-piperidin-1-ylmethyl)-piperazin-2-one or
(*S*)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-[(2-methoxy-ethylamino)-methyl]-piperazin-2-one
or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

22. A compound according to claim 1 selected from the group consisting of 1-[4-(2-Chloro-pyrimidin-4-yl)-benzyl]-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazine-2,3-dione, 1-(4-Amino-quinazolin-7-ylmethyl)-4-[4-(5-chloro-thiophen-2-yl)-benzyl]-piperazine-2,3-dione, 1-[4-(5-Chloro-thiophen-2-yl)-benzyl]-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2,3-dione, 1-(4-Amino-quinolin-7-ylmethyl)-4-[4-(5-chloro-thiophen-2-yl)-benzyl]-piperazine-2,3-dione, 1-[1-(2-Chloro-pyrimidin-4-yl)-piperidin-4-ylmethyl]-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazine-2,3-dione, 1-[3-(5-Chloro-thiophen-2-yl)-allyl]-5-(S)-isopropyl-4-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-piperazine-2,3-dione, 1-[3-(5-Chloro-thiophen-2-yl)-allyl]-4-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-piperazine-2,3-dione, 1-[3-(5-Chloro-thiophen-2-yl)-allyl]-4-(4-pyridin-3-yl-benzyl)-piperazine-2,3-dione, 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(4-pyridin-4-yl-benzyl)-piperazine-2,3-dione, 1-[4-(6-Amino-pyridin-3-yl)-benzyl]-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazine-2,3-dione, 1-[3-(5-Chloro-thiophen-2-yl)-allyl]-4-[4-(1-oxy-pyridin-3-yl)-benzyl]-piperazine-2,3-dione, 1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-5-(S)-isopropyl-4-(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-ylmethyl)-piperazine-2,3-dione, 1-[3-(5-Chloro-thiophen-2-yl)-allyl]-5-(S)-isopropyl-4-(4-pyrimidin-4-yl-benzyl)-piperazine-2,3-dione, 1-[3-(5-Chloro-thiophen-2-yl)-allyl]-4-(4-pyrimidin-4-yl-benzyl)-piperazine-2,3-dione or 1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-piperazine-2,3-dione or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

23. A compound according to claim 1 selected from the group consisting of

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid;

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester;

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid ethyl ester;

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)--oxo-piperazine-2-carboxylic acid 2-pyrrolidin-1-yl-ethyl ester;

1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)--oxo-piperazine-2-carboxylic acid 2-pyrrolidin-1-yl-ethyl amide;

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester;

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester;

(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester;

(S)-[1-(4-Amino-quinazolin-7-ylmethyl0-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-yl] acetic acid;

(S)-[1-(4-Amino-quinazolin-7-ylmethyl0-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazin-2-yl] acetic acid tert-butyl ester;

(+/-)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methyl-piperazin-2-one;

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methyl-piperazin-2-one;

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methyl-piperazin-2-one;

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isopropyl-piperazin-2-one;

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isopropyl-piperazin-2-one;

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isobutyl-piperazin-2-one;

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isobutyl-piperazin-2-one;

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-piperazin-2-one;

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-piperazin-2-one;

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-isopropylaminomethyl-piperazin-2-one;

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-methyl-piperazin-2-one;

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-methyl-piperazin-2-one;

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isopropyl-piperazin-2-one;

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isopropyl-piperazin-2-one;

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one;

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one;

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one;

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one;

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-methyl-piperazin-2-one;

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-methyl-piperazin-2-one;

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isopropyl-piperazin-2-one;

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isopropyl-piperazin-2-one;

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one;

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-isobutyl-piperazin-2-one;

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one;

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one;

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-methyl-piperazin-2-one;

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-methyl-piperazin-2-one;

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isopropyl-piperazin-2-one;

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isopropyl-piperazin-2-one;

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isobutyl-piperazin-2-one;

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-isobutyl-piperazin-2-one;

(R)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one;

(S)- 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-6-methoxymethyl-piperazin-2-one;

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-ylmethyl)-piperazin-2-one;

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[1-(2-dimethylamino-pyrimidin-4-yl)-piperidin-4-ylmethyl]-piperazin-2-one;

N,N-Dimethhyl-N4{[(chlorobenzo[b]thiophene-2-sulfonyl)-2-(keto)piperazin-1-yl]methylpiperdinyl]} cyanoguanidine;

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-{1-[2-(2-hydroxy-ethylamino)-pyrimidin-4-yl]-piperidin-4-ylmethyl}-piperazin-2-one;

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[1-pyrimidin-4-yl)-piperidin-4-ylmethyl]-piperazin-2-one;

3-{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazol-4-yl}-3-methyl-butyric acid ethyl ester;

(R)-2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid amide;

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid ethyl ester;

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4,5,6,7-tetrahydro-benzothiazol-2-ylmethyl)-piperazin-2-one;

(R)-4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-1-(4-pyridin-3-yl-thiazol-2-ylmethyl)-piperazin-2-one;

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-hydroxy-4,5,6,7-tetrahydro-benzothiazol-2-ylmethyl)-piperazin-2-one;

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid isopropyl-methyl-amide;

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid amide;

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-6,7-dihydro-5H-benzothiazol-4-one oxime;

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid methoxy-methyl-amide;

2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-6,7-dihydro-5H-benzothiazol-4-one;

(R)-2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-methoxymethyl-6-oxo-piperazin-1-ylmethyl]-thiazole-4-carboxylic acid dimethylamide;

1-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester;

1-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester;

1-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester;

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-hydroxymethyl-1-(1-methyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one;

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-carboxylic acid methyl ester;

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one; and

4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one;

or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

24. A compound according to claim 1 selected from the group consisting of 1-4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]- piperazin-2-one ditrifluoroacetate,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3-(S)-methoxymethyl-piperazin-2-one ditrifluoroacetate,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3-(S)-propyl-piperazin-2-one ditrifluoroacetate,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-3-(S)-methyl-piperazin-2-one ditrifluoroacetate,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]- piperazin-2-one ditrifluoroacetate,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]-3-methoxymethyl-piperazin-2-one ditrifluoroacetate,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]-3- methyl-piperazin-2-one ditrifluoroacetate,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-2H-pyrazol-3-ylmethyl]-piperazin-2-one ditrifluoroacetate,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-2H-pyrazol-3-ylmethyl]-3-(S)-methyl-piperazin-2-one ditrifluoroacetate,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-2H-pyrazol-3-ylmethyl]-3-(S)-methoxymethyl-piperazin-2-one ditrifluoroacetate),

1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(3-chloro-phenyl)-4H-[1,2,4]triazol-3-ylmethyl]-(s)-3-methoxymethyl-piperazin-2-one ditrifluorocetate,

1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(3-chloro-phenyl)-4H-[1,2,4]triazol-3-yl-methyl]-piperazin-2-one ditrifluorocetate,

1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl)-4H-[1,2,4]triazol-3-ylmethyl]-piperazin-2-one ditrifluorocetate,

1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl)-4H-[1,2,4]triazol-3-ylmethyl]-(s)-3-methoxymethyl-piperazin-2-one ditrifluorocetate,

1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(4-chloro-phenyl)-4H-[1,2,4]triazol-3-yl-methyl]-(s)-3-methoxymethyl-piperazin-2-one ditrifluorocetate,

1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl-[1,3,4]oxadiazol-2-ylmethyl]-(s)-3-methyl-piperazin-2-one ditrifluorocetate,

1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl)-4H-[1,2,4]triazol-3-ylmethyl]-(s)-3-methyl-piperazin-2-one ditrifluorocetate,

1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl)-4H-[1,2,4]triazol-3-ylmethyl]-(s)-3-methoxymethyl-piperazin-2-one ditrifluorocetate,

1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl-[1,3,4]oxadiazol-2-ylmethyl]-piperazin-2-one ditrifluorocetate,

1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(4-chloro-phenyl)-4H-[1,2,4]triazol-3-yl-methyl]-piperazin-2-one ditrifluorocetate,

1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl-[1,3,4]thiadiazol-2-ylmethyl]-piperazin-2-one ditrifluorocetate,

1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl)-[1,3,4]thiadiazol-3-ylmethyl]-(s)-3-methoxymethyl-piperazin-2-one ditrifluorocetate,

1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl)-[1,3,4]thiadiazol-3-ylmethyl]-(s)-3-methyl-piperazin-2-one ditrifluorocetate,

1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl)-[1,3,4]thiadiazol-3-ylmethyl]-(s)-3-propyl-piperazin-2-one ditrifluorocetate,

1-(4-Amino-quinazolin-7-ylmethyl-4-[5-(5-chloro-thiophen-2-yl)-[1,3,4]thiadiazol-3-ylmethyl]-(s)-3-ethyl-piperazin-2-one ditrifluorocetate,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-chloro-thiophen-2-yl)-pyridin-2-ylmethyl]-piperazin-2-one tritrifluoroacetate,

1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-pyridin-5-yl-methyl]-piperazin-2-one tritrifluoroacetate,

4-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one ditrifluoroacetate,

4-[5-(5-Chloro-thiophen-2-yl)-4H-[1,2,4]triazol-3-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one ditrifluoroacetate,

[5-(5-Chloro-thiophen-2-yl)-[1,3,4]oxadiazol-2-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,

4-[5-(5-Chloro-thiophen-2-yl)-oxazol-2-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one ditrifluoroacetate,

4-[5-(5-Chloro-thiophen-2-yl)-[1,3,4]thiadiazol-2-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one ditrifluoroacetate,

4-[5-(5-Chloro-thiophen-2-yl)-2H-pyrazol-3-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one ditrifluoroacetate or

1-[5-(5-Chloro-thiophen-2-yl)-isoxazol-3-ylmethyl]-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one ditrifluoroacetate

or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

25. A compound according to claim 6 selected from the group consisting of 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-(R)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-(6-Chloro-thieno[2,3-b]pyridine-2-sulfonyl)-6-(R)-methoxymethyl-1-(1H-pyrrolo [3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-(5-Chloro-1H-indole-2-sulfonyl)-6-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-(S)-isopropyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-(S)-isopropyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-(S)-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-one,
4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-(S)- propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-one,
4-(5-Chloro-1H-indole-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-[3-(5-Chloro-thiophen-2-yl)-isoxazol-5-ylmethyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
4-[4-(5-Chloro-thiophen-2-yl)-benzyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-benzyl]-piperazin-2-one,
1-(4-Amino-quinazolin-7-ylmethyl)-4-[4-(5-chloro-thiophen-2-yl)-benzyl]-piperazin-2-one,
4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(7-methyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one or
4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-(7-methyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one
or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

26. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier.

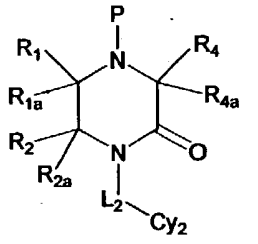
27. A method for treating a patient suffering from a physiological condition capable of being modulated by inhibiting activity of Factor Xa comprising administering to said patient a pharmaceutically effective amount of a compound according to claim 1.

28. A method for treating a patient suffering from a physiological condition capable of being modulated by directly inhibiting activity of both Factor Xa and Factor IIa comprising administering to said patient a pharmaceutically effective amount of a compound according to claims 21 and 23.

29. A method for treating a patient suffering from a physiological condition capable of being modulated by directly inhibiting activity of both Factor Xa and Factor IIa comprising administering to said patient a pharmaceutically effective amount of a compound according to claim 16.

30. A method for treating a patient suffering from a physiological condition capable of being modulated by directly inhibiting activity of both Factor Xa and Factor IIa comprising administering to said patient a pharmaceutically effective amount of a compound according to claim 17.

31. A compound of formula III

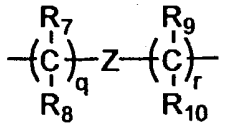


III

wherein P is H or a nitrogen protecting group;

R_1, R_{1a}, R_2, R_{2a}, R_4 and R_{4a} are independently selected from hydrogen, carboxy, alkoxycarbonyl, $Y_1Y_2NC(O)$-, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl, or R_1 and R_{1a}, R_2 and R_{2a} or R_4 and R_{4a} taken together form O or S; or R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, or heterocyclenyl group; or R_{1a} and R_{2a} are absent and R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form an aryl or heteroaryl group; or R_1 and R_{1a} taken together with the carbon atom through wrich they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_2 and R_{2a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_4 and R_{4a} taken together with the carbon atom through wrich they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group;

L_2 is absent or a group of formula



Cy_2 is selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcycloalkyl, optionally substituted fused heteroarylcycloalkenyl, optionally substituted fused heteroarylheterocyclyl and optionally substituted fused heteroarylheterocyclenyl;

R_5 is hydrogen, optionally substituted alkyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, $R_6O(CH_2)v$-, $R_6O_2C(CH_2)x$-,$Y_1Y_2NC(O)(CH_2)x$-, or $Y_1Y_2N(CH_2)v$-;

R_6 is hydrogen, optionally substituted alkyl, optionally substituted aralkyl or optionally substituted heteroaralkyl;

Y_1 and Y_2 are independently hydrogen, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl or optionally substituted heteroaralkyl, or Y_1 and Y_2 taken together with the N through which Y_1 and Y_2 are linked form a monocyclic heterocyclyl;

R_7, R_8, R_9 and R_{10} are independently selected from hydrogen, hydroxy, alkoxy, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aralkyl and optionally substituted heteroaralkyl, provided that only one of R_7 and R_8 or one of R_9 and R_{10} is hydroxy or alkoxy, and further provided when R_7, R_8, R_9 and R_{10} is hydroxy or alkoxy, then the hydroxy or alkoxy is not α-substituted to a N, O or S in Z;

Z is absent or is selected from optionally substituted lower alkenylene, optionally substituted lower alkynylene, O, S(O)p, -C(O)-, NR_5, -NR_5C(O)- and -C(O)NR_5-;

x is 1, 2, 3 or 4;

v is 2, 3 or 4; and

q and r are independently 0, 1, 2 or 3, provided that q and r are not both 0,

provided that when R_1, R_{1a}, R_2, R_{2a}, R_4 and R_{4a} are independently selected from hydrogen, carboxy, alkoxycarbonyl, $Y_1Y_2NC(O)$-, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl then L_2 is absent, or when

R_1, R_{1a}, R_2, R_{2a}, R_4 and R_{4a} are independently $Y_1Y_2NC(O)$- then Y_1 and Y_2 are independently hydrogen, optionally substituted alkoxy or optionally substituted aryloxy, but Y_1 and Y_2 are not simultaneously hydrogen, or when

R_1, R_{1a}, R_2, R_{2a}, R_4 and R_{4a} are independently selected from hydrogen, carboxy, alkoxycarbonyl, $Y_1Y_2NC(O)$-, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl then Z is –C(O)-.